UNITED STATES FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

PART 15 HEARING:
DRAFT GUIDANCES RELATING TO THE REGULATION OF HUMAN CELLS, TISSUES, OR CELLULAR OR TISSUE-BASED PRODUCTS

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WILLIAM MURRELL
Info Health Global

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ADAM KATZ
International Federations for Adipose Therapeutics and Science

KAREN NICHOLS
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P R O C E E D I N G S

(9:00 a.m.)

DR. WITTEN: Good morning to both the attendees in the conference center and those viewing the hearing through our live webcast. Welcome to the second day of the Part 15 hearing on the draft guidances related to the self regulation of human cells, tissues, and cellular and tissue based products.

I'm Dr. Celia Witten, Deputy Director of the Center for Biologics Evaluation and Research. I will serve as the presiding officer for this hearing. Before we begin I will provide a few housekeeping announcements. Those of you who were here yesterday have heard these announcements yesterday, but I'm repeating them for the sake of the attendees who have just joined us for the day today.

Please turn off any mobile devices as they may interfere with the audio in this room. We ask that all attendees sign in. Upon sign in you will be given a name tag indicating whether

you were speaking or attending without speaking. The hearing is scheduled from 9:00 a.m. until 5:00 p.m. today. Restrooms are located in the lobby. Today we are planning for a 20 minute break in the morning session and a 15 minute break in the afternoon session. Please remember not to eat or drink in the auditorium, and if you do bring something in to take out your trash. Today's lunch break is scheduled from 12:19 p.m. to 1:34 p.m. There are a variety of lunch options in the cafeteria in the basement of this building. As we're on a tight schedule we'll resume promptly.

The purpose of the hearing today is to obtain broad stakeholder input on the following four draft guidances related to the regulation of human cells, tissues, and cellular and tissue based products, or HCT/Ps. Those guidances are the same surgical procedure exception, questions and answers regarding the scope of the exception, minimal manipulation of human cells, tissues in cellular and tissue based products, human cells, tissues in cellular and tissue based products from

adipose tissue regulatory consideration, and homologous use of human cells, tissues, and cellular and tissue based products draft guidance for industry and staff.

I'd like to provide some brief background on the regulatory framework. In 1997 FDA first announced our propose approach to the regulation of HCT/Ps. FDA then engaged in notice and comment rulemaking. The resulting regulatory framework became fully effective May 25, 2005. Since that time FDA has issued a number of guidance documents to further assist stakeholders in implementing the regulations. We have received requests from stakeholders for further clarification, including to explain further our current thinking related to whether an HCT/P is subject to premarket approval. Specifically, stakeholders have asked questions about the same surgical procedure exception and the meaning of homologous use and minimal manipulation.

In addition we have received a number of questions related to products derived adipose

tissues. FDA issued these four draft guidances in response to these requests, thus the draft guidances are intended to provide clarity around our established regulatory framework for HCT/Ps.

FDA will consider the information we obtain from the speakers participating in public hearing and from information submitted to the dockets, both before and after the hearing, as we finalize these four draft guidances. As we described in the Federal Register Notice announcing this hearing, we are interested in comments on the scope of the four draft guidances, including the particular topics covered, the particular questions posed, whether there are additional issues for which guidance would be helpful, and whether FDA's recommendations for each topic are sufficiently clear and consistent within and across the documents to provide meaningful guidance to stakeholders. In addition, FDA welcomes comments that will enhance the usefulness and clarity of these documents.

So I've already introduced myself, but

I'm now going to ask the FDA panel members to introduce themselves.

MR. WEINER: I'm John Barlow Weiner, Associate Director for Policy for the Office of Combination Products at FDA.

DR. LARD: Good morning, I'm Sherry Lard; I'm the Associate Director for Quality Assurance in the Center for Biologics, and the Product Jurisdiction Officer.

DR. ANATOL: I'm Rachel Anatol, Associate Director for Policy in the Office of Cell, Tissue, and Gene Therapy in the Center for Biologics.

MS. MALONEY: Good morning, I'm Diane Maloney, Associate Director for Policy in the Center for Biologics Evaluation and Research.

MS. ZAVAGNO: Good morning, I'm Denise Zavagno; I'm Senior Counsel. I'm in the Office of the Chief Counsel at FDA?

MS. MALARKEY: Good morning, I'm Mary Anne Malarkey; I'm the Director of the Office of Compliance and Biologics Quality at the Center for

Biologics Evaluation and Research, FDA.

MS. KRUGER: Good morning, I'm Angela Kruger; I'm an Associate Director for Guidance and Regulation in the Office of Device Evaluation in the Center for Devices and Radiological Health.

DR. WITTEN: Thank you. There is much interest in this area. I'm now going to talk a little bit about the speakers and the agenda. We accepted request to speak on a first come, first serve basis and every speaking slot was allocated. To those who wish to speak but could not be accommodated, we thank you for your interest and your understanding. We encourage you to submit your full written comments to the Division of Dockets Management following the instructions in the Federal Register Notice for this meeting. We will carefully consider all comments submitted to the Docket as we work to finalize the guidance documents.

We have a very full agenda, which includes of 90 scheduled presentations. In order to ensure that we can complete this agenda, I will

go over some ground rules. Each registered speaker has been given a five or eight minute time slot on the agenda, depending on whether they represent the interest of a single stakeholder or multiple stakeholders respectively. Give the very full agenda we request that each speaker keep to the allocated time so that we are able to keep to this tight schedule and allow everyone on the schedule an opportunity to speak. If a speaker ends early we intend to move on to the next speaker. We will need to stick to this timeframe and I thank you in advance for doing so. We have let speakers know ahead of time about the importance of sticking to the allotted.

And for the speakers, I'll lust let you know that the yellow light will flash when you have a minute left so that you can take that into account in wrapping up. Speakers can provide additional comments that go beyond their allotted time by submission to the dockets.

This part 15 hearing is informal and the rules of evidence to not apply. No participant

may interrupt the presentation of a registered speaker. Only FDA panel members will be allowed to ask questions of the speakers. FDA may call a speaker back for questions or clarification during the allotted times for panel questions, assuming time allows and the presenter remains available.

Public hearings under Part 15 are subject to FDA policies and procedures for electronic media coverage of FDA public administrative proceedings. Representatives of the electronic media may be permitted subject to certain limitations to video tape, film, or otherwise record FDA's public administrative proceeding, including the presentations of the speakers today.

This meeting will be transcribed and the transcript will be made available at the website specified in the Federal Register Notice for this meeting. The docket will be open until September 27 and we encourage you to submit your full written comments to the Division of Dockets Management following the instructions in the

Federal Register Notice.

Again, given the full agenda, we request that each speaker keep to their allotted time so that we're able to keep to the tight schedule. We thank you for your interest and participation today and look forward to a productive public hearing.

We'll proceed with the presentations. The first speaker represents the Foundation for the Accreditation of Cellular Therapy.

SPEAKER: Excuse me, ma'am -- doctor? We're going to have to reboot this computer; we have a technical problem.

(Recess)

DR. WARKENTIN: Good morning. Thank you for the opportunity to present this morning. I am Phyllis Warkentin, Professor of Pathology of Pediatrics at the University of Nebraska Medical Center and Chief Medical Officer of the Foundation for the Accreditation of Cellular Therapy.

The mission of FACT is to improve the quality of cellular therapies through pure

developed standards, education, and voluntary accreditation. FACT's goals are first to promote quality patient care and laboratory practice through a valid accreditation process that includes all three phases of cell collection, laboratory processing and storage, and clinical practice, including cell administration. Implicit in this comprehensive approach is open by directional communication to ensure that cell procurement and manufacturing are informed by clinical outcomes, safety, efficacy, and adverse events. The second goal is to improve treatment outcomes, and the third is to foster research and continued development of the field of cellular therapies.

FACT is the standards and accreditation arm of ASMBT, ISCT and NetCord, and collaborates in standards development internationally with the Joint Accreditation Committee of ISCT and EPMT, known as JACIE.

All FACTS standards are developed by a consensus of experts based on published research

and clinical data to the largest extent possible. The input of regulatory bodies, legal, professional organizations, and the public, including patients, is sought and is vital. Standards that may exceed regulatory requirements but are not less rigorous. FACT has three current active sets of standards, the hematopoietic cell therapy standards, core blood banking standards, and the first edition of common standards for cellular therapy.

FACT common standards are those fundamental standards applicable to any cell type, cell source, clinical application, phase of product development, or clinical trial. These standards require quality management instituted as early as possible in product development as a mechanism to ensure process controls for facilities, personnel, equipment, procedures, testing, labeling, and transport. These standards recognize various outcome measures, depending on phases of study, with safety as the first measure. There are two anticipated roles for the FACT

common standards. First, to serve as the basis for primary certification in early phase products or applications. And, second, to serve as a foundation for discipline specific standards in collaboration with relevant experts.

The first such discipline is the discipline of immune effector cell therapies. These standards are currently under final review, were developed in response to numerous clinical trials of products associated with unique and significant toxicities, manufactured in a limited number of facilities, but administered in diverse clinical settings. The standards unique to immune effector cells will be added to the requirements for accredited hematopoietic clinical settings. However, the primary target audiences are the clinical units outside of traditional transplant units, such as leukemia and oncology units.

FACT does have several specific comments to the draft guidance. First, we believe FDA should fulfill its responsibilities to protect patients in search of cellular therapies. We

support our parent society, ISCT, in its position on unproven cell therapies and agree on the importance of providing adequate education for patients. Development of professional standards and voluntary accreditation can play an important role in providing a bridge from basic research to clinical application. There is precedent for this in the same surgical procedure exception draft guidance wherein FDA has noted that hospitals must follow guidelines of the Joint Commission on Accreditation of Healthcare Organizations, or JCAHO, for tissue storage as a reason to permit the same surgical procedure exception.

Experts in respective fields who hold themselves to a higher standard are in the best position to maintain quality and safety, to collect appropriate data, and to complete clinical trials. We are to develop mechanisms to reduce and minimize the burden of clinical trials to get promising therapies to patients. Examples of how this could be accomplished include shared validation studies for microbial testing and the

use of accredited clinical sites for early clinical trials.

Second, tiered unified approach to HCT/P regulation fails to acknowledge the complexity of some tissues with multiple native functions in many cell types. It is difficult to strictly categorize complex tissues such as adipose tissue as only structural or cellular. Some possible solutions include determination of homologous use could be not dependent upon the initial categorization as whole tissue, but allow for cells and structural elements to be considered individually. The term "such HCT/P" could then be used to apply to either the cells or the structural elements depending on the intended use and the recipient. The term "homologous use" could be broadened to include any function or functions performed in the donor, not only a single basic function.

Third, the agency could specify and recognize the standard of care exceptions for certain procedures that have long been in place

without such tissue regulation, those procedures in which data exists related to the practitioners, procedures and safety. For example, breast reconstruction. Third, there appear to be a few inconsistencies that we have noted that would benefit from clarification. For example, the definition for homologous use. Although various phrases are used throughout the documents, such as perform the same basic function or functions, and perform one or more of the same basic functions, examples seem to ignore the concept of more than one function for a specific tissue. Secondly, the following example is also confusing to many people, it is considered non homologous to adipose tissue in breasts as the function of breast is lactation, ignoring the role of fat in support and shape. But it is homologous to put islets into the liver, although the liver function is certainly not glucose homeostasis.

Fourth, we suggest that the agency expand expectations for cord tissue to include which regulations apply and when they apply. For

example, whole cord tissue collected, cryopreserved, and stored as whole tissue when the future use is unknown, compared with cord tissue processed first and then cryopreserved. International harmonization is also important to facilitate product development and worldwide availability of products.

Thank you.

DR. WITTEN: Thank you. Our next speaker represents Info Health Global.

MR. MURRELL: Good morning distinguished Chairperson and assembled members of the Committee. I would like to thank you for organizing this hearing to hear comments on the four proposed draft guidances. We appreciate your attentiveness and willingness to listen to our observations and suggestions. It is no doubt a Herculean effort to balance our requests with the FDA mission.

I am Bill Murrell and I am the Executive Director of Info Health. We are a healthcare consultancy that assists facilities with

development of clinical programs, regulatory compliance, quality management systems, and if desired, preparation for accreditation of their cellular and biological treatment programs and storage.

Although we've only been in business for two years we have experienced a great response, especially from the practitioners in the area of musculoskeletal space. As experienced in-processing storage and treatment with cellular and biological agents is limited in comparison to bone marrow and cord blood and other hematologic and non hematologic uses and applications of HPC. The thirst to better serve or deliver products to patients that are compliant with harmonized international standards holds great interest in many of our practitioners. Our clients are found in the Americas, Europe, and Asia currently. In addition, I am an actively practicing orthopedic surgeon.

My exposure and entry into the area of regulation has stemmed from a decade of trying to

advance clinical studies, replicating the work that has been completed elsewhere, utilizing biological agents to augment current orthopedic procedures in a non university academic private practice. In an attempt to garner approvals to go forward with both self funded and sponsored studies programs had to be designed that approval bodies cannot say no. And this largely occurred because of -- we instituted programs modeled after cord blood to get approvals. The specific area that is of great interest to me and many in our space, that is largely unsolved, is the ability to repair and regenerate synovial joint articular cartilage. Globally it is a problem of epidemic proportions where we routinely see persons undergoing joint replacements in their fourth and fifth decades of life. The long-term impact of this activity is already being with patients undergoing revision surgeries in subsequent decade of life, the cost of which is growing exponentially and likely to be unsustainable.

Today I will limit my comments and

recommendations to two of the four draft guidances. I will start with minimal manipulation. Physical culture of autologous chondrocytes for implantation for articular cartilage defects predates both the current regulation in the U.S. as well as Europe. The treatment has been found to be safe, effective and affordable. This change, however, with the hospital exemption rule in Europe and with increased regulation resulting in a tenfold increase in price. The therapy was also approved in the U.S. with rules less oppressive than the standards of today and certainly less than the draft guidances that we are considering currently.

Despite having an approved product globally, the application of this technology unfortunately does not make it to patients as the coverage by third party payers is quite scare. Herein lies the problem, we have treatments but we cannot use them. This makes little sense. As healthcare practitioners we held accountable for providing solutions that today when patients are

far better educated and are demanding that we progress, innovate, and treat their underlying conditions, this is a great opportunity and promise of regenerative medicine.

One of the theoretical risks for high risk assignment of culture cells is the formation of tumors. In the case of ACI no tumors have been seen clinically since being instituted with over a 20 year positive track record. Additionally, culture expanded MSCs have also been used worldwide since the late 1990s. And although the data is limited studies today have shown an impressive safety profile, especially when used in an autologous fashion. A total of 149 patients in the first studies with 1-11.5 years follow up demonstrated no AEs or severe adverse events. Systematic review by Peters in 2013 based on 884 treatments in 8 studies reached the conclusion that interarticular injections of culture expanded MSCs are safe. Currently there are active treatment programs in Australia, Japan, and Singapore utilizing culture expanded MSCs for

treatment of both traumatic chondral injury as well as degenerative disease. And I am sure that the Committee is quite aware of the recent Australian TGA regulation allowing physicians to not only culture and administer autologous cells, but also to use them in homologous and non homologous fashions.

So what are we recommending? We recommend that we follow some of the recommendations from the REGROW bill, the Senate REGROW bill on Section 351(b), approval for cellular therapies, specifically allow non homologous use of minimally manipulated autologous cells that are appropriately produced, allow also for more than minimal manipulated autologous cells, i.e., culture cells that are not genetically modified and appropriately produced.

We'd also like you to consider creating separate autologous guidelines, or better yet leave things alone. Specifically, state registration of products and treatment programs require accreditation of programs similar to what

hospitals currently use, JCI, using best available international guidelines. Also allow state medical boards to regulate physician activities. Additionally, we recommend the creation of a task where all stakeholders, especially patients and patient advocacy groups can make commentary, doctors, scientists, FDA, industry, Congress, state medical bodies, and accreditation bodies.

Recommendations on homologous use. Currently there's a lack of evidence for either side. Our specific recommendation is leave the draft guidance open until further conclusive evidence is available from both sides. If action is taken, some of the recommendations from the REGROW bill specifically allow for non homologous use of minimally manipulated autologous cells that are appropriately produced, allow for more than minimally manipulated autologous cells cultured that are not genetically modified and appropriately produced. The power to heal is within every human being, we must think about our patients first. Cellular therapies, including

culture cell autologous products are safe and have a long standing safety record even if produced by physicians. Culture cellular products are low risk products and are different than pharmaceuticals, especially when autologous and therefore should be regulated differently. Homologous use guidance should be left open until further evidence has been provided.

Thank you. (Applause)

DR. WITTEN: Thank you. Our next speaker represents the Institute for Regenerative and Cellular Medicine.

DR. RODRIGUEZ: Good morning. My name is Ricardo Rodriguez and I am a plastic surgeon. I was on the faculty at Yale Medical School and now have a private practice with a teaching appointment at Johns Hopkins. I have a grant from the Maryland Stem Cell Research Foundation to track SVF cells in vivo that have been injected into radiated breasts.

My comments will be restricted to the FDA draft guidance for adipose tissue and levels

of risk. The FDA states because connective tissue provides structure and support to the body FDA considers connective tissue, including adipose tissue, to be a structural tissue. This statement is not supported by the FDA's cited authority used in the guidances, "Junqueira's Basic Histology Textbook and Atlas".

In the chapter dedicated to connective tissue Junqueira recognizes that connective tissue has other functions than providing structure and support. It classifies connective tissue as follows: 1. Connective tissue proper. 2. Embryonic connective tissues. 3. Specialized connective tissues. The specialized connective tissues are defined by the principal specialized functions. They are blood, reticular connective tissue, adipose tissue, bone, and cartilage. Although the primary function of some types of connective tissue is to provide structure and support to the body, connective tissue has a wide variety of functions that depend on the types of cells and the different classes of fibers

involved. For example, blood is a specialized connective tissue consisting of cells and fluid whose principal function is transport. It is a connective tissue that is not structural tissue. Reticular connective tissues have a backbone composed of a delicate network of reticular and collagen III fibers with attached fiber blasts that hold the organ together. Examples of reticular connective tissue are liver, bone marrow, pancreas, and lymph nodes. It is connective tissue that is not structural tissue. In fact the FDA explicitly classifies these connective tissues as not structural because they serve predominantly metabolic or other biochemical roles in the body, including endocrine functions.

Adipose tissue is yet another specialized connective tissue that has structural elements but is not solely defined by them. Junqueira, the FDA's own cited authority lists the many functions of adipose tissue in Chapter 5. In the first paragraph it lists a storage depot and metabolic energy regulatory functions of adipose

tissue. In the second paragraph it highlights the importance of adipose tissue as circulatory endocrine organ responsive to nervous and hormonal stimuli. In the third paragraph it lists the space occupying and cushioning physical properties of adipose tissue.

Furthermore, in the summary key points section of the chapter, used as an authority source, it states that defining cells of adipose tissues are adipose sites. Cells of adipose tissue are supported by reticular fibers. The FDA's cited authority cites clearly and emphatically that adipose tissue is connective tissue who's defining function is metabolic and non structural co-existing with structural features. A Google Scholar search of all available on line medical databases for the primary function of adipose tissue returns 538,000 journal articles. The vast majority refer to the non structural endocrine and circulatory properties of adipose tissue. A search for the exact match, or the phrase primary function of

adipose tissue yielded the following: It was long believed the primary function of adipose tissue was energy storage. In fact stromal adipose tissue is a complicated endocrine organ. This is critically important because it goes to the core of determining what constitutes minimal manipulation and what is homologous use of adipose tissue. CFR 1271.3 states, homologous use means 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. Section 1271.3 correctly acknowledges that an HCT/P may have more than one function. Junqueira, the FDA cited authority for these guidelines, states unequivocally that this is a true fact for adipose tissue. FDA guidance must reflect this fact. Currently it does not.

And now I'd like to comment on levels of risk. This mischaracterization of the nature of tissues also undermines the ability of a risk tier framework to adequately assess risk. There is no

scientific or rational basis for treating an allogeneic, cultured, engineered IPS cell and an autologous and none expanded SVF cell as having identical risk profiles. The tragedies we heard of last Thursday were not caused by SVF cells misbehaving. They were caused by practitioners misbehaving. A general practitioner instead of a board certified ophthalmologist injecting an eyeball poses a far greater and immediate danger that whatever cells or even FDA approved drug may be in the syringe, that is the real problem that brought us there. Any meaningful solution must target this problem effectively. Studies and registries are a great start to verify claims of safety, but they happen only after the fact. They are also prone to self-reporting errors. Accreditation of stem cells facilities and practitioners is a better solution. Any practicing physician here in this audience knows that accreditation of practitioners and healthcare facilities is the industry standard for maximizing patient safety before, during, and after therapy.

Periodic audience and the specter of losing one's credentials are powerful motivators and deterrents.

Specialist societies, like IFATS and the ASPS welcome the opportunity of working together with accreditation agencies, such as AAAASF, that accredits surgery centers and the AABB and ISCET present here to work together to help the FDA solve the problems that brought us here.

Thank you. (Applause)

DR. WITTEN: Thank you. Our next speaker represents the International Federations for Adipose Therapeutics and Science.

DR. KATZ: Good morning. My name is Adam Katz; I'm a Professor in the Department of Surgery in the Division of Plastic Surgery at the University of Florida. Clinically I practice a wide spectrum of plastic and reconstructive surgery and I also direct a laboratory engaged in basic as well as translational and clinical research related to adipose derived therapies. I have been involved in this field of research since

1993 and I was a member of the team that published the seminal peer reviewed paper describing the multi lineage potential of adipose derived stromal cells. This was published in 2001, and according to Google Scholar it has now been cited over 6000 times.

For purposes of full disclosure I have also founded two for profit companies, both of which have worked with the FDA and currently have two FDA approved clinical studies ongoing.

Today, however, I speak on behalf of the International Federation for Adipose Therapeutics and Sciences, or IFATS. I speak on behalf of them as a society cofounder, a member of the board of directors, and chair of the regulatory affairs committee. IFATS is a not for profit entity and was founded in 2003, and since that time attendance at our annual meetings has grown by nearly tenfold, drawing members from 40 countries around the world. The society brings together scientists, clinicians, translational researchers, and regulatory and biotech representatives to

discuss the latest advance in adipose tissue biology.

In addition to leading adipose biologists, the membership also includes practicing cardiologists, immunologists, neuroscientists, plastic and reconstructive surgeons, orthopedists, and vascular surgeons to name a few. As such, we believe the society has a unique expertise and wide ranging perspective to potentially serve as a resource and partner for examining and structuring policies related to adipose derived therapies in particular.

Like all in this room, IFATS is first and foremost committed to the ethical translation of adipose derived treatments and to ensuring the prioritization of patient safety in the application of these new treatments. In the context of patient care specifically this is guided by an oath taken by every physician in the United States that in some form or another includes the concept of primum non nocere, or first do no harm. The society also recognizes,

supports, and advocates adherence to the principles of the Belmont Report, which summarizes the ethical principles and guidelines for the protection of human subjects in research.

We certainly appreciate the time and effort that the FDA has put forth on the guidance documents related to the use and translation of adipose products in particular, and we are highly aware of the difficult challenge which the agency is faced with to find a balance between issues of patient safety and treatment efficacy with those of progress, innovation, ethical clinical research, the practice of medicine, and the autonomy of patients, which centers around the long standing doctrine of informed consent that provides a patient the right to direct his or her care in general in the use of his or her own cells and tissues in specific.

In addition to written comments previously submitted and those that will follow these hearings, I would like to take the time we have here today to focus the remainder of our

comments on one particular core issue that we believe is at the heart and influences all other guidance interpretations related to fat. In short, IFATS's request that the FDA reconsider its position that adipose tissue is exclusively or even primarily categorized as a structural tissue. The FDA guidance specifically states that adipose tissue is, "Typically defined as a connective tissue". Because connective tissue provides support and structure to the body, the FDA considers connective tissue, including adipose, to be structural. And in support of this position, the guidance references basic histology text. However, if one examines this reference in detail, and many others like it, one will find that blood, bone marrow, pancreas, and lymph nodes, along with adipose tissue, are all considered connective tissues, and specialized connective tissues at that.

Based on the logic proposed by the FDA then these same tissues, namely blood, lymph node, and pancreas, which are all histologically

classified as connective tissue, should also be considered to be primarily structural because, "They are connective tissues and connective tissues provide support and structure to the body." Of course we do not advocate that blood be considered a structural tissue. And yet in the guidance document related to minimum manipulation of HCT/Ps, the FDA specifically lists tissues such as blood, pancreas, and lymph nodes as non structural tissues. This leads one to ask why are some connective tissues considered to be structural by the FDA, that is adipose, but others in the same histological categorization, such as blood and pancreas, are not. This categorization is inconsistent and confusing at best, and arbitrary at worst. It is unsupported by fact and even contradicted by the very source referenced by the FDA in their guidance document.

With respect to function, the guidance document further states, "For purposes of applying the regulatory framework we, the FDA, generally consider adipose tissue to be a structural tissue

with characteristics for reconstruction, repair, or replacement that relate to its utility to cushion and support the other tissues in the subcutaneous layer and skin." However, based on existing biological, scientific, and clinical realities, we submit that this blanket characterization of adipose tissue as solely a structural tissue is too simplistic and does not reflect clinical reality or establish scientific fact.

Indeed, I could spend the entire eight minutes today speaking on details related to the non structural functions and activities of adipose tissue alone which have previously been mentioned to include inflammation, angiogenesis, vascular genesis, cell differentiation, metabolism, and more. In fact, adipose tissue is described as an endocrine organ by the very source that is referenced by the FDA in the guidance documents.

In conclusion, the FDA's current guidance documents acknowledge the different components of adipose tissue, and thus, by

implication, acknowledge that fat does more than cushion and support. Given the wide range of functions attributable to adipose tissue we request that the classification of adipose tissue be expanded from one of an exclusively or primarily a structural tissue to one that is both, or either structural and/or non structural. And we further propose that the FDA regulate a given adipose derived product based on the specific cell type or types and/or the specific matrix component or components that are included in the product, and to do so in the context of a specific intended use.

I'd like to thank the FDA for arranging the workshop last week, which was quite informative for me, and also for these hearings and for the opportunity to speak today.

(Applause)

DR. WITTEN: Thank you. The next speaker represents the International Society for Cellular Therapy.

DR. NICHOLS: Good morning. My name is

Karen Nichols. I am Chief Regulatory Officer of the International Society for Cellular Therapy. I am here today presenting brief, prepared remarks on the four draft guidances before us. Specifically, as we've heard, those draft guidances are homologous use of HCT/Ps, minimal manipulation of HCT/Ps, HCT/Ps from adipose tissue, regulatory considerations, and the same surgical procedure exception under 21 CFR 27115, Q&A.

The International Society of Cellular Therapy, ISCT, is a global society of clinicians, regulators, researchers, technologists, and industry partners with a shared vision to translate cellular therapy into safe and effective therapies to improve patients' lives worldwide. We are focused on preclinical and translational aspects of developing cell based therapeutics in three key areas of translation, academia, regulatory, and commercialization. Through strong relationships with global regulatory agencies, academic institutions, and industry partners ISCT

drives the advancement of research into standard of care. ISCT thanks FDA for the opportunity to provide formal feedback on these draft guidances. ISCT support efforts that provide more clarity, consistency, and transparency in regulatory environments for HCT/Ps. And the topics covered by the draft guidances are highly relevant and timely for today's environment. ICT found a lot to like in these documents.

In the draft guidance on homologous use ICT requests that specific examples are provided of advertising materials that illustrate objectionable claims. Ideally claims that have already been evaluated by agency and deemed to be indicative of advertising that promotes non homologous use and also a consideration of how these examples might be evaluated if the advertising did not originate from the same source as the product. Would these claims be viewed the same way in light of the products' non homologous use with the same impact on the manufacturer themselves?

ICT also requests that the agency provide specific examples of the triggering behavior that might occur to demonstrate manufacturer's objective intent that an HCT/P is being offered for non homologous use. For example, would this include hands on demonstrations in addition to oral or written statements by the manufacturers or its representatives?

ISCT appreciates the clarification provided for the definition between structural and cellular non structural tissues. As already illustrated and heard here in the last day or so, a structural tissue contains cellular elements, and both may play an equally important role in product function, and perhaps both need to be considered when determining the level of manipulation each is subjected to.

Similar to the amniotic membrane example and other examples already in the draft guidance, we request that an example be provided regarding the processing of umbilical cord tissues,

specifically the extraction and processing of umbilical cord to remove cells and/or other components for potential further therapeutic use.

To highlight the contrast for more than minimally manipulated we request FDA provide an example of minimally manipulated adipose tissue in this section of the guidance. For example, as suggested by the homologous use example B1, adipose tissue recovered and processed for cosmetically filling voids in subcutaneous space of the face or hands could also be minimally manipulated. In light of the recent presentations there are potentially several ideas and/or suggestions that have been offered to the Committee to this point in this hearing that could be added to this guidance to provide practical examples for the readers.

We suggest that you consider facility registration and periodic inspection of facilities that remove adipose tissue based products from an individual and return that adipose derived tissue to the same person at a different time. This

would provide oversight for HCT/P tracking, raw material control and handling for facilities, which is vital, particularly if they may not be otherwise accredited. It is critical that all tissue and product contact material are absolutely traceable and subject to a degree of quality oversight that seeks to minimize or eliminate the risk of product mix up and/or contamination.

Similarly we ask you consider registration and inspection oversight for surgical sites that again remove cell or tissue based products from one individual with a plan to return them to the same individual at a different time for the same reasons as noted in the previous slide. Again this would provide oversight for the HCT/P tracking, raw material control and handling, for facilities where that will be important, and again, particularly if they're not otherwise accredited. It is vital that all the tissue and product contact materials are absolutely traceable and subject to a degree of quality oversight that seeks to minimize or eliminate the risk of product

mix up and/or contamination, and to have practical, if not absolute assurance and support of both product and patient safety.

In conclusion, as previously stated, ISCT supports efforts that provide more clarity, consistency, and transparency in regulatory environments for HCT/Ps. We also suggest that these draft guidances, combined with current regulatory pathways, are part of an existing framework that should be correctly used prior to creating parallel perhaps redundant product advancement pathways as suggested by the recently proposed REGROW legislation, and in which the society has provided its current thinking on this potential legislation and a recent press release as of August of 2016.

ISCT requests that U.S. regulators engage with the government personnel involved in this legislative effort to ensure consistency between these draft guidances, current regulatory pathways, and the proposed REGROW legislation to facilitate safe, effective, and economical

cellular therapies are provided to the patients who actually need them. On September 8 Dr. Domenici provided the agency with ISCT's view on unproven cellular therapies. Finalizing these draft guidances will provide more tools that legitimate manufacturers can use as well as provide a better ability to identify the purveyors of those unproven therapies.

Thank you for allowing ISCT to participate in this public meeting. (Applause)

DR. WITTEN: Thank you. Our next speaker represents the International Society for Stem Cell Research.

DR. ROOKE: Good morning. I am Health Rooke, Scientific Director of the International Society for Stem Cell Research. I think the FDA for this opportunity to present and to participate in the discourse between the many different stakeholders represented here at this hearing.

The ISSCR is an international membership organization representing over 4000 stem cell researchers from more than 55 countries. We have

members from academia, industry, and clinical settings. The ISSCR was established to promote professional and public education in all areas of stem cell research and application, to foster the exchange of information and ideas relating to stem cells, to encourage the field, and to facilitate the clinical application of what is learned.

Our members are extremely interested in harnessing the promise of stem cell research to transform human health worldwide and to do this through the understanding of how our cells and tissues work, understanding disease and identifying new therapeutic approaches, and in the development of stem cell and cell derived treatments for repair or replacement. The ISSCR is committed to delivering scientifically sound and evidenced based stem cell treatments. And we speak to these scientific principles today. We do have concerns that stem cell treatments are being marketed directly to consumers without the safeguards in place to ensure likely safety and efficacy of experimental treatments, or indeed

truthfulness of the claims about so-called proven therapies. This phenomenon has been referred to as stem cell tourism, but is not restricted to individuals travelling internationally. And the marketing of purported stem cell treatments with little to no evidence of clinical utility and in some cases complete disregard of the known cell or tissue biology is also prevalent here in the United States. We therefore welcome a role for the FDA in overseeing clinical applications of human cells tissue or cell and tissue based products.

In 2008, in an update earlier this year, the ISSCR released our guidelines for our members for the clinical translation of stem cells. The ISSCR guidelines for stem cell research and clinical translation promote a rigorous scientific and (inaudible) medical process and aim towards a good use of resources to get the best medicines to patients. The guidelines bring together guidance for laboratory research and translation for this research to the clinic under five core principles,

integrity of the research process, which relies heavily on independent review and oversight, including regulation, patient welfare, respect for research subjects, transparency, and social justice. The ISSCR guidelines demand robust standards for pre clinical and clinical research as well as independent review and oversight. As potential treatments move through clinical testing towards the market the guidelines focus considerable attention on the preclinical and clinical phases of research, calling for studies to produce persuasive evidence of clinical promise before trials go forward and calling for rigorous evaluation for safety and efficacy before marketing approval of a stem cell treatment.

We have heard a lot about the complexity of biological products, the wide variety of methods used in processing, manufacture, and delivery. And recognizing these challenges and the resultant uncertainty, the ISSCR guidelines advocate for stringent review and oversight and that wherever possible potential stem cell

treatments be tested for safety and efficacy in formal clinical trials before approval. There will always be unknowns in moving into human testing, however the balance of risk and potential benefits can be improved with a sound understanding of the underlying biology and an understanding of the anticipated mechanism of action. Prudent use of resources demands that even when risk is modest studies should rest on sound scientific evidence of expected efficacy. Striking the right balance between facilitating patient access to new treatments and rigorous evaluation is an ongoing challenge for us and for regulatory authorities, however, it is important that exemptions or shortcuts do not undermine this rigorous testing.

The ISSCR guidelines also highlight the responsibility of all groups communicating stem cell science and medicine to present accurate balance reports of expectations progress and setbacks. The provision of accurate information about stem cell based interventions and about

risks, limitations, possible benefit, and available alternatives is essential in the delivery of quality healthcare. In this regard I raise the importance of how the term stem cell is used. A cell should only be defined as a stem cell if rigorous criteria are met where there is demonstrated capacity for the cells that self renew and to differentiate into mature progeny. For example, we've heard a great deal about mesenchymal stem cells, yet there is considerable skepticism in the field about whether mesenchymal cells manifest the so-called stemness, and whether mesenchymal cells from different tissue sources have the same properties. There is a very high perceived value of what stem cells can do that derives directly from the concept that stem cells are highly versatile and medically valuable. And we believe in this promise. This term stem cell has strong marketing appeal and should be used accurately. There are many examples of false or misleading product promotion using the term stem cell to promote an intervention without evidence

of the cell's potential. There are many different types of stem cells that come from different places in the body and these cells differ in their properties and potency. Moreover, the context of the cell, where it came from, as well as how it is treated and where it is placed in that treatment, will impact its behavior and claimed function should be evaluated rigorously for a given product and indication.

In closing I would like to reiterate the comments of Jonathan Kimmelman who spoke on behalf of the ISSCR last week at the FDA workshop. Biomedical research is a collective enterprise and the FDA plays an important role in balancing the varying perspectives of researchers, clinicians, industry, and patients, and ensuring that clinical applications are evidence based. We welcome this partnership and offer our support and expertise to the FDA as they address the comments received about the current guidance documents and also in looking forward to future guidance to accommodate scientific advances, new challenges, and evolving

social priorities.

Thank you. (Applause)

DR. WITTEN: Thank you. Our next speaker represents the National Center for Health Research.

DR. FOX-RAWLINGS: Thank you for the opportunity to speak today. My name is Dr. Stephanie Fox-Rawlings. I am a Senior Fellow at the National Center for Health Research. Our research center analyzes scientific and medical data to provide objective health information to patients, providers, and policy makers. We do not accept funding for the drug or medical device industry.

Before coming to the National Center for Health Research I worked as a developmental neuroscientist at the Children's National Medical Center. My project was to understand how cells respond to damage and how neuro stem cells respond to the changes in their environment to promote recovery. If my work in the laboratory has taught me anything it's that cells, especially stem

cells, are extremely dynamic. They continuously react to and are modified by their environment. Small changes can greatly affect the way cells behave. For example, exposing cells to different growth factors or signaling molecule, or even varying the oxygen level can change the number of cells and what they become. Cells and tissues are much more complicated than drugs and biologics. They are not a simple compound or a single protein that can be easily characterized in a lab test. A cell is a living, changing organism and they move throughout the body. They can make other cells change their behavior. Stem cells can change, even transform into new cells types. Because of this cells and tissues have an amazing and exciting potential to heal people and cure disease. But just as these cells have the potential to help they also carry the potential for harm. That's why cells and tissues should be properly tested and regulated before widespread use in patients.

The FDA's guidance provide a

scientifically logical distinction between which cells and tissue treatments need stricter regulation and which do not. The guidances require cells or tissue products where cells are changed or used in a new function to be clinically tested to ensure they are safe and effective. This is reasonable because we cannot assume that they will function in this new way in this environment, or that they would not do something unexpectedly to cause harm. This regulatory process, if it was equivalent to the simpler drugs and biologics, the fact that cells and tissues are more complicated does not mean that they should be less regulated. To the contrary, their complexity should warrant an increased need for testing. The FDA proposes less stringent regulation for cell and tissue treatments for rare diseases or diseases that currently lack approved treatment options. Fortunately the FDA already has mechanisms in place for reviewing those types of urgently needed treatments, but these mechanisms must not be weakened.

We don't know how many people are helped or harmed by many of the cell therapies currently being marketed. How many of the clinics providing treatments have studies to back up their success rates or side effects? In some cases the harms are sensational enough to make the news, but when treatments are harmful there's often little incentive to report them to the FDA. And in some cases neither patients nor physicians will realize that a complication is caused by the treatment. Even if a treatment isn't dangerous an ineffective treatment harms patients because it is so expensive. And of course many of these treatments offer little besides false hope. At worst clinical side effects can occur, such as what we've heard with the tumors and vision loss.

That's why clinical trials are absolutely necessary. Patients should be able to make an informed decision about their treatment with information based on data and good science, not just hype and hope. Regulation will also ensure that the cells that clinics claim to use

are actually the cells that are put into a patient's body. It can ensure that the chemicals used to process these cells are safe for this purpose. Regulation and rigorous scientific testing benefits patients now and in the future. If there are too many cases of patients who are harmed or too many treatments fail because some clinicians use untested treatments, the whole field could be disregarded as snake oil. Not only will patients be harmed by bad treatments, but also by the failure to develop real treatments.

In conclusion, we strongly support the FDA's regulation of cell and tissue products. The guidances are reasonable. Through regulation the FDA can protect patients and encourage innovation and the development of new treatments based on scientifically sound science. However, enforcement will be critical to stop untested and potentially harmful therapies.

Thank you for your time and consideration of our views. (Applause)

DR. WITTEN: Thank you. Our next

speaker is representing the Cord Blood Association.

DR. KURTZBERG: Good morning. My name is Dr. Joanne Kurtzberg and I'm honored to speak on behalf of the Cord Blood Association. I'm qualified to speak in this capacity as a pediatric transplanter, cord blood banker, cell therapist, and president of the CBA.

The CBA is a young and vigorous international nonprofit organization. CBA members include both public and private family banks, industry partners, foundations, and individuals in and served by the cord blood community.

Cord blood was first used in 1988 as a source of HLA match to related donor cells in a five year old patients with fanconi anemia undergoing transplantation to treat bone marrow failure. The transplant, a first in man experiment performed in a child with minimal preclinical data, was successful. The patient, now 33 years old, is living a normal life 27 years later. Importantly, his blood and immune systems

are fully comprised of his sister's cord blood cells. This transplant paved the way for the fields of cord blood banking and transplantation. Today there have been more than 35,000 cord blood transplants performed and more than 160 cord blood banks have been established worldwide. Public inventories approach 700,000 units and private inventories more than 4,000,000 worldwide.

Cord blood was the first (inaudible) to put a stem cell product to be regulated by the FDA. To date seven public cord blood banks have successfully completed BLAs. Lessons learned from the cord blood BLA process should inform regulation of other cell therapies going forward. For example, cells do not necessarily expire. Stability protocols performed to extend expiration dates sacrifice unique cell products that cannot be replaced.

Excessive environmental monitoring adds little if any value to manufacturing that is performed in a closed system when appropriate qualification testing is performed and

specifications are met. The delivery of babies, although sanctioned by nature, is not sterile, not controlled, and a highly variable process. Cord blood and cord tissue are sourced from this disadvantaged position. Regulatory flexibility is critical to enable the use of these valuable products. Cord blood and cord tissue derived products have enormous potential for the development of novel cell based therapies that will have a critical role in the fields of cellular therapies and regenerative medicine.

To this end the CBA emphasizes the following points related to the proposed guidances:

1. Cord blood is not a back up stem cell. While it does contain small numbers of blood stem cells the majority of cells are different shaded blood cells. Some of these other cells have therapeutic value, but do not act through engraftment, tissue integration, or differentiation. Rather, they are effector cells acting through pure (inaudible). As such, we

strongly encourage the FDA to consider these mechanisms of action as homologous.

2. The regulatory framework, which is largely focused on review of drugs, is not sufficient for review of cellular therapies. We encourage the FDA to modify these regulations to address the unique properties of cells.

3. The designation of minimal or more than minimal manipulations should be risk based with consideration of clinical indication, writ of administration, and with the complexity of manufacturing of the product. If the cells are prepared aseptically and only exposed to FDA approved for human use free agents and devices, manufacturing should be considered minimally manipulated.

4. The designation of 1271 products, including autologous cells or tissues, as well as cells and tissues from first and second degree relatives is outdated. If HLA matched is the operative in this reasoning then the guidance should state that related HLA identical or

hapiloidentical products are included.

5. The FDA should consider a pathway for cellular therapy similar to that already established for hematopoietic stem cell and solid organ transplantation. Emerging therapies could be prepared and delivered in accredited facilities, monitored under IND if indicated, and outcomes could be reported to a registry, such as the CIBMTR. Expanded access studies could also be used to monitor safety. This is one way to get therapies to patients more quickly while continuing to monitor safety and efficacy.

The CBA has the following specific comments related to two of the guidances under discussion today: First, the guidance for HCT/Ps from adipose tissue doesn't acknowledge MSCs or mesenchymal stromal cells, the primary cell therapy extracted from adipose tissue. These cells represent a major therapeutic resource and should be considered homologous when used to exert paracrine effects. This has relevance not only to MSC derived from adipose tissue, but MSC from cord

tissue, bone marrow, and others.

I will end with comments about the homologous use guidance, which is particularly relevant for cord blood bankers and for patients who may benefit for autologous and allogeneic cord blood therapies extending beyond hematopoietic reconstitution. An example would be the treatment of young children with cerebral palsy with autologous cord blood. In the draft guidance for homologous use FDA states in Section 31C, "A manufacturer provides HPCs derived from cord blood with a package insert stating that cord blood may be infused intravenously to differentiate into neuronal cells for treatment of cerebral palsy. This is not homologous use because there is insufficient evidence to support that such differentiation is a basic function of these cells in the donor." In this instance FDA incorrectly assumes that the mechanism action of these cells in treating kids with CP is reintegration of cord blood stem cells capable of differentiating into neuronal cells. If this were the case we would

agree that that was non homologous use. However, in this therapy autologous cord blood cells are acting through signaling mechanisms that are innate properties of the infused cells and that act on endogenous cells in the patient through paracrine homologous mechanisms.

So we have an autologous not more than minimally manipulated product used for homologous or non homologous use. If the FDA accepts that this use is homologous then administration of autologous cord blood for CP, which is not more than minimally manipulated, would be viewed as practice of medicine and regulated under 1271 as a 361 product. However, if the FDA designates the use as non homologous and expects a BLA then who gets the BLA? Does each family or private bank go through the BLA process for this indication? Does the treating institution obtain the BLA? Does a public bank get the BLA? The list of questions goes on and one and the CBA welcomes the opportunity to engage in meaningful conversation with the FDA regarding these questions.

The CBA is committed to bringing effective cord blood and cord tissue derived therapies to patients as safety and efficiently as possible and thanks the FDA for the opportunity to raise these issues. We look forward to the FDA's feedback on our comments.

Thank you. (Applause)

DR. WITTEN: Thank you. Our next speaker is from The Cure Alliance.

MS. ROSS: Thank you for the invitation to speak today. My name is Shelley Ross and I'm President of The Cure Alliance, a nonprofit group of leading translational researchers, surgeons, innovators, and those who support our efforts to end human suffering by curing chronic, debilitating, and fatal diseases. Our number one goal is to eliminate barriers to discovery and accelerate potential cures from the lab to the bedside.

I am not a scientist. Most of my career has been in broadcast news, CBS, NBC, 17 years at ABS News, where I worked with Diane Sawyer, Peter

Jennings, George Stephanopoulos, Robin Roberts, and more. As the Executive Producer of Good Morning America I covered four wars and broadcasted live from our Times Square studio during the 9/11 attacks. Today I am here as a witness from another battlefield -- cancer. In August 2012 I found a tiny lump in my breast that was indeed malignant. High fives for early detection, but because of my cancer type and discovery of a mutated BRCA gene I faced six months of chemotherapy followed by a double mastectomy and oophorectomy. By bilateral mastectomy was April 16, 2013, the day following the bombings at the Boston Marathon. An occupational hazard -- I still mark time by news events.

My surgery went well. Breast amputations with simultaneous reconstruction, tissue expanders held in place by internal slings made of cadaver tissue that had been radiated, freeze dried, and repurposed. Monday, one week after the Boston bombing, I caught another news

report on an amazing recovery of the 31 year old dance instructor whose foot had been blown off. She was sitting up, smiling and talking about when she could start dancing again with a prosthetic. I could barely move, feeling toxic and weak. I called my surgeon, how is the dance instructor doing so much better than I? She said, well, the dancer didn't undergo five and a half hours of surgery, her surgery didn't follow six months of chemotherapy, and you're not 31 anymore. Cruel, right? (Laughter) It turned out that toxic feeling wasn't related to any of the above. My body had failed to integrate those structural slings which had been disintegrating and rotting inside my chest. I was no longer on a garden variety breast cancer journey.

Just four weeks after my doubt mastectomy I underwent another surgery to remove all reconstruction materials. When I awoke I learned my chest cavity was sanitized with showerheads for more than an hour. The area now needed to heal. I can't really call it healing.

Without any breast tissue remaining from my collarbone down there was only one outcome, my skin scarred to my ribcage. I was no longer a candidate for reconstruction, and adding to my personal misery index, the side effects from chemotherapy included multiple tears in the rotator cuffs of both shoulders. By now dressing, washing, combing what was left of my hair, became a painful kabuki dance. Trying to heal was exhausting and frustrating.

As weeks of pain turned into months I came to the stark realization, I was disabled. As I looked in the mirror I saw the devastating reflection, something that resembled a plucked chicken with two broken wings. Until that point fighting cancer involved clear and time tested decisions. Now I was in uncharted territory. Incredibly, within our ranks of The Cure Alliance was a remarkable surgeon in Milan who had invented a simple sterile closed loop technology to micro-fractionalize one's own lumpy adipose fat into a fine injectable. Basically there would be nothing

to reject. When I first spoke to this doctor about his technology he was using it for facial reconstructions, bad knees, shoulders, and wound healing. A few months later he phoned and said, I have treated a patient just like you and it was a success. That's all I needed, just one. Any risks were mine to take.

On December 30, 2013 in Milan I had 370 ccs of my own fat drawn from my abdomen and back, then micro- fractionalized, and injected into my breasts. This was followed by reconstruction and permanent implants. As a bonus the surgeon injected 5 ccs of micro-fragmented fat in one shoulder, 7 in the other. By mid afternoon I was back in my hotel room, 3 days later I attended a birthday party in London, and back home I felt whole again. For a long time I thought the treatment had not worked on my shoulders. It had turned out to be a delayed response. After nine months I've suddenly realized I could do this, I could do this pain free.

(Laughter) As a journalist and

producer I suspect I am a bit more resourceful than the average patient, which is why I'm here today, to respectfully ask the FDA to revise the draft guidance which will essentially force people like me to unnecessarily bear the pain and disabling scars of a disease we already fear could take our lives, a disease that not so long ago sentenced untold numbers of women to a life of disfigurement and social isolation. This FDA draft guidance states that clinicians can use fat grafting in the breast without restrictions only if it involves what the FDA says in the main function of the breast, lactation. If used for breast reconstruction clinicians would have to file IND applications, biologic license, be subject to extensive reporting requirements. Really? Why? That fat transfers can be used safety and effectively in breast reconstruction has been known for over 100 years. That a woman's breasts are not just for babies has been known for at least 200,000 years.

(Laughter) (Applause) And what of the 2600 American men who battle breast cancer each year? Simple fat transfers are often their safest and simplest option.

The protection of patients has been long been guided by the principles of the Belmont Report, which clearly distinguishes between medical practice and research of humans subjects. The fact that a procedure is experimental in the sense of new, untested, or different, does not automatically place it in the category of research. Research is designed a hypothesis. In all the Belmont Report identifies three ethical principles, respect for human subjects, beneficence, do no harm, justice. And injustice occurs when some benefit to which a person is entitled is denied without good reason, or when some burden is imposed unduly. Please do not restrict fat transfers for those who need breast reconstruction. Let's address safety and efficacy without building barriers and embrace this

explosive pace of progress in a way that is more respectful and just.

Thank you. (Applause)

DR. WITTEN: Thank you. Our next presentation is from the Plastic Surgery Foundation.

DR. CEDERNA: Thank you very much for the opportunity to speak today. My name is Paul Cederna and I'm President-Elect of the Plastic Surgery Foundation. I'm also Chief of Plastic Surgery at the University of Michigan and a Professor in biomedical engineering.

The Plastic Surgery Foundation was founded in 1948 and the mission of the PSF is to foster innovation in plastic surgery and to improve the quality of life of our patients through research, development, innovation, discovery, charity care, and public awareness. We support a number of different programs, including our visiting professors program, our international scholars program, and donations from the PSF go forward to support volunteers in plastic surgery

who go to underserved areas to provide patient care. We have a budget of about $3.1 million a year and with that budget we support research, educational programs, workshops, and research or development.

During the past year we awarded 36 grants for about $800,000; 20 percent of these grants were in the area of fat grafting and stem cell research. And since 2011 we've actually funded 25 grants, for a grand total of about $600,000 in the area of fat grafting. We've also supported three research fellowship awards in the area of fat grafting to support young investigators as they begin their academic careers. And these research awards go to some of the finest institutions in America. We've supported research in a lot of different areas trying to understand better the impact of fat grafting and stem cells on radiated bone, skin regeneration, scleroderma, radiated skin, primary fracture healing, and even areas such as peripheral nerve repair, diabetic feet, aging

tissue, and of course as we just heard about, breast reconstruction. And a lot of very high quality research has come out of this funding. One of the studies by Dr. Kronowitz out of MB Anderson and his colleagues actually published this paper recently in plastic and reconstructive surgery, looking at lipofilling of the breast and safety related to that procedure, and demonstrating there's actually no increased risk of breast cancer in patients who have undergone fat grafting to the breast.

And there have been a number of similar studies which have published in our literature as well, including studies from Dr. Delay, studies from Heath Sharvay, studies from Dr. Catherine Gail, and Jean Pittet, and of course from Regina Rogotti, all supporting the safety and efficacy of fat grafting of the breast in the presence of post mastectomy breast reconstruction.

The PSF's mission though has been to pursue fat grafting in the safety of that in a number of different arenas. And so we have two

safety initiatives that we have funded over the past few years, and since 2011 we've actually spent $400,000 in developing these safety initiative. The first is the cancer occurrence after fat transfer or CRAFT study. The Plastic Surgery Foundation funded this and the coordinating center was out of University of North Carolina with Memorial Sloan Kettering, Wash U, MD Anderson Cancer Center, and University of Chicago participating. And we understood that fat transfer is increasingly popular in the treatment of breast cancer patients and we wanted to ensure that this was safe in the presence of breast cancer. And so looking at women with stage 1 through 3 invasive ductal carcinoma we looked at cancer recurrence in that situation. And with this large study population we identified no increased risk of breast cancer in patients undergoing fat transfer to the breast.

We've also been very committed to forming additional registries for the purposes of understanding the safety and efficacy of fat

grafting in our patients as well. One of them is a general registry of autologous fat transfer or graft. We do understand that there is a lack of consensus regarding fat grafting methods and analysis of outcomes. We know there's a lot of different outcomes and we know that patient satisfaction measures haven't been carefully evaluated in the past. So the purpose of this registry is as a quality improvement initiative to collect as much data as possible to understand techniques of fat grafting, outcomes of fat grafting, and their implications on patient safety more widely. So this is a nationwide registry with a web accessible database. The aims are, as I said, to prospectively determine early and late complication rates and patient reported outcome measures of satisfaction. Our all procedures module, which looks at fat grafting to any area of the body was launched in 2015 and all of the members of the ASPS performing fat grafting have been encouraged to enter their data into this database. We've had a breast module presence

since 2014 to capture fat grafting into the breast. Our inclusion criteria are any patient of any variety getting fat grafting for any purpose and our exclusion criteria are those patients who are undergoing dermal fat grafting or any composite grafts of any variety.

We're collecting all sorts of data so that we can understand the implications of this much better. We're looking at fat harvesting techniques, processing techniques, and then looking at satisfaction measures. We are collecting a lot of data over time, including six week data, six month data, one year data, and two to three year data. So hopefully we should have a very clear understanding of the optimal ways of performing fat grafting and the outcomes related to it.

As of July 2016 we have 150 members of ASPS who have registered to participate in the registry. We have more than 1500 patient visits so far. So for a very young and early registry I'm excited about the progress it's making and

look forward to the numbers increasing dramatically in the coming years. And as you see we've had a steady increase in the numbers of patients who are being entered into the registry, which should give us very significant abilities to understand fat grafting a little bit better, optimal techniques, and approaches.

Since 2011 the Plastic Surgery Foundation as invested more than $1 million in fat grafting research and patient safety initiatives. We're focused on providing the highest quality of safe and effective care for our patients at all times. We're interested in any body trying to investigate the safety of fat grafting, the efficacy of those outcomes, and patient safety related to it. And we offer ourselves as potential partners with the FDA to help work this out going forward.

I appreciate the opportunity to participate in these sessions today.

Thank you very much. (Applause)

DR. WITTEN: Thank you very much for

your comments. It's now time for questions from the FDA panel to the speakers, so I'll ask my colleagues if they have questions, otherwise I'll start.

DR. ANATOL: So this question is for ISCT. Thank you. In your presentation you asked that we provide examples of advertising materials in the homologous use guidance. Do you have specific examples in mind of advertising materials or what may be considered advertising materials?

DR. NICHOLS: Not off the top of my head. I would say that in general advertising materials we were thinking of as we were considering this request was there's a lot of electronic media out there that's being distributed and things get repurposed, if you will. They get re tweeted, they get moved around, they become -- where do you find the order after a while, I guess. So it was more along the lines of also trying to understand kind of the cascade effect of what happened with advertising as well.

DR. ANATOL: Thank you.

MS. MALONEY: I had question for Info Health Global, the speaker. In your presentation you spoke about the lack of evidence and gathering additional evidence. Can you just say a little bit more of what evidence you're talking about and what that might show?

MR. MURRELL: That's really in reference to the homologous use guideline. I think that as many of the talks have demonstrated that really there's just not a lot of credible evidence, like the body of evidence to support or refute this guideline. It's just not present. And what my suggestion is, is that we reserve judgment on this particular guideline to another time until we have more evidence on either side of the question, because I just don't think that there is a great deal of evidence available.

MS. MALONEY: Okay, thank you.

MS. ZAVAGNO: I also have a question for you though. I just want to push because I want to understand this better. I had the same question, when you're talking about a lack of evidence you

mean -- because it's homologous use that you're talking about -- is it that we don't know how a specific cell or tissue works and you want to wait until we get more evidence that will work -- I mean because homologous use means, you know, it acts the same way in the donor as in the recipient usually, right, or it has the same function. So I don't understand what kind of evidence you want us to wait for.

And then you also you said that we should leave the guidances open for further conclusions. How long would you want the FDA to wait?

MR. MURRELL: That's a very good question, but my example using say cultured cells, to date they're -- from the studies that have been it's only about 800 patients that we have data, especially for adipose tissue. And that would be considered in this guideline to be non homologous use. And so my comment is really stating that we just don't have the evidence to say that it's risky for our patients. We don't have evidence

long-term to say that it is absolutely safe. But at the same time certainly the clinical utility of these treatments are burgeoning, the data is burgeoning, it's growing. And so my thought is really until we have more data, whether it be coerced studies, prospective studies, or randomized control trials, that demonstrate either that the use of these cells are safe and efficacious, I would say that we just don't have adequate evidence on either side of the question, whether we should or shouldn't at this point. And so that's a -- I hope I've shed a little bit more light on that.

MS. ZAVAGNO: Yes, you did. Thank you very much.

DR. WITTEN: I have a couple of questions for some of the speakers who spoke on topics specifically related to the guidances. One is for the speaker from the International Federation for Adipose Therapeutics and Science.

So a number of your comments would speak to the minimal manipulation guidance, although not

directly. And I'm wondering if you can give us some idea of what you would consider minimal versus more than minimal manipulation as it relates to adipose tissue. If you can provide some examples in each category.

DR. KATZ: I just referenced the minimum manipulation document once in the context of certain tissues listed by the FDA as being non structural in that document, but according to the histological reference as being a connective tissue. And so logically, based on the documents presented to us at this point those tissues would be categorized as structural by say the adipose tissue guidance document, but in the minimum manipulation document they're listed specifically as non structural tissues. And so I was just pointing out an inconsistency.

DR. WITTEN: Okay, thank you. And I also have a question for the speaker from the Cord Blood Association, which is similar perhaps in nature. I'm just wondering if you can provide -- many of your examples related to the question

about homologous versus non homologous use. And if you can give some examples of how you see that definition applying to cord blood.

DR. KURTZBERG: Yes. So the obvious is that when cord blood is used for hematopoietic reconstitution that's easily understandable as homologous use. You're taking the blood stem cells from cord blood in the context of all the other cells and using them to rescue marrow after myeloablative therapy. But the stem cells represent probably.03 or less percent of the actual cells in cord blood. And there are other populations of cells that have therapeutic value. One example is the CD14 cells, which are monocyte-like cells which produce a lot of different cytokines and other methods for paracrine signaling. And those cells have therapeutic effects in animal models of asphyxia or hypoxic injury, myelination models where they can induce re- myelination. And they're not themselves doing those activities, what they're doing is signaling endogenous cells in those

models or in the organism that can then act. And we think that that is homologous because that is what those cells also do in vivo and should be considered as homologous activity in therapeutics.

DR. WITTEN: Thank you. END OF AUDIO 219

MS. MALONEY: I have a question for the speaker from the Plastic Surgery Foundation.

On one of your slides you spoke about the wide range of outcomes. Can you just say a little bit more about that?

DR. CEDERNA: Yes, absolutely. When we think of the outcomes following fat grafting, we do fat grafting all over the body. We do it following traumatic injuries to the foot, the knee, the ankle, the back, the chest, the head, everywhere. Some of those areas have contaminated tissues in the region, some of them have been radiated, some of them have fractures underneath, some of them have a lot of different biologic processes going on that potentially can impact the survival of fat after transfer. And so

understanding that a little bit better and understanding the areas where it may be effective and may not be effective, understanding the implication of that on the surrounding tissues is really important to us.

And so that's why one of our graft registry modules is all of the body, not just the breast, but all of the various areas in understanding all of the indications for use of fat.

MS. MALONEY: Thank you.

MS. MALARKEY: I have a question for the speaker from ISCT. Actually a couple of questions I think. Oh, I'm sorry, I apologize -- from FACT. My apology.

DR. WARKENTIN: Me?

MS. MALARKEY: Yes. FACT. (Laughter) FACT, not fat, not fat. You ad mentioned this recognition of standard of care exemptions and had given -- that the FDA consider that for certain procedures that have been in place without tissue regulation. You mentioned breast reconstruction

as one example. Do you have any other examples of exactly what you mean by that?

DR. WARKENTIN: So I think some of the cellular therapies that we use in oncology and transplantation of hematopoietic cells are more considered standard of care. And as the professional societies have worked to develop the preparative regimes and the integration of preparative regime with cell source, these have become more standard treatments for certain diseases. That carries with it some ability to recover costs in that kind of care. So it's thinking more along that line and in the more cellular therapies outside of hematopoietic. I think obviously the fat was the best example I could think of.

MS. MALARKEY: Thank you. One other question. You had talked about cord tissue and suggested that we expand expectation for cord tissue in the guidance and gave some examples. My question is are you speaking of autologous or family related or allogeneic that you would like

examples of?

DR. WARKENTIN: So for cord tissue I think a lot of cord blood banks are collecting cord tissue as aside to collecting the cord blood cells into a unit. And so the comment could apply to either family related or to unrelated donor cord tissue. The confusion comes around the amount of regulatory oversight necessary if you're doing very minimal manipulation and storage up front, not knowing what the intended use will be in the future. You may or may not even know if it's to be used for related or unrelated setting. The concern is that the amount of regulation in that activity not be so burdensome that it can't be done, but yet the source which will be adequate 10 years now to be a certifiable source for a product that's developed at a later time. So it's a balance between the regulation that occurs up front when something (inaudible) versus what might happen later on when there might be more regulatory oversight as compared with those folks who do a lot of processing and manipulation up

front before they store the cord tissue.

MS. MALARKEY: Thank you very much.

DR. ANATOL: I have another question for FACT also. In your presentation you suggested that we broaden the term homologous use to include any function or functions performed in the donor, not just the basic function. Can you give us an example or two of anything you had in mind in particular?

DR. WARKENTIN: So I was thinking specifically in the case of adipose tissue where there are certain structural characteristics, cellular characteristics, and there are many, many functions to that complex tissue.

DR. ANATOL: Okay. Okay, thanks.

DR. WITTEN: Okay. Any more questions? Otherwise I think we'll wrap it up. We're going to thank the speakers. We'll wrap it up and we're resuming at 11:08. So be back in your seats promptly at 11:08.

(Recess)

DR. WITTEN: So I'd like everyone to

take their seats. Can you all take your seats please? Are we ready to start? The first speaker, I'm not sure if he's signed in or not, Waldo Acebo. Is Waldo Acebo here? Okay. We're going to -- how about Rebecca Baergen? Thank you.

DR. BAERGEN: Good morning and thank you for allowing me to speak today. My name is Rebecca Baergen. I am a Professor of Pathology and Laboratory Medicine at Weill Cornell Medical College and Attending Pathologist and Chief of Obstetric and Perinatal Pathology at New York Presbyterian Hospital. I'm the author of several books and many book chapters on placental and perinatal pathology and co-author of pathology of the human placenta.

I am here to address the draft guidelines on minimal manipulation and homologous use as they relate to the amniotic membrane. The draft guidelines on minimal manipulation assumes that the amniotic membrane has a main function, which is to act as a cover or barrier. As such it is regulated as a purely structural tissue. The

draft guideline on homologous use also characterizes the amniotic membrane as a structural tissue, although it acknowledges a slightly more expanded list of functions of the amniotic membrane, to include covering, protecting, serving as a selective barrier for the movement of nutrients between the external and in utero environments, and retention of fluids in utero. It is my opinion that the premises underlying the proposed regulatory scheme are scientifically flawed.

The amniotic membrane has multiple functions in vivo, both structural and non structural, and one is not more important than the other. In addition to the functions listed in the draft guideline documents the amniotic membrane also produces bioactive factors and molecules, including growth factors, cytokines, leukotrienes interleukins, and a number of enzymes, chemokines, and related regulatory proteins, including anti inflammatory proteins. It secrets extracellular matrix, it serves as a substrate for supporting

growth of epithelial cells and modulates inflammation and serves as an anti scarring agent. Indeed, it is interesting to note that the placenta, unlike other organs, does not scar.

Based on review of peer reviewed literature amniotic membrane has been processed into tissue allografts and performs multiple functions in the recipient. Recognized functions and applications of the amniotic membrane include modulating inflammation, reducing scarring, pain relief, accelerated wound healing, promoting epithelialization and cell growth. The functions of the amniotic membrane in a transplant recipient are a direct result of the native tissue's inherent biological and physical properties. As an example, the amniotic membrane's ability to mediate wound healing, anti inflammation, and anti scarring are due in part to the extracellular matrix which is a component of the amniotic membrane. The extracellular matrix is composed of secreted collagen and glycoproteins. And in addition to providing structural support the

extracellular matrix contains molecules that are essential for cell signaling and growth factor mediated function, such as wound healing.

The amnion also inhibits the expression of transforming growth factor beta which activates the fiberglass responsible for fibrosis and scarring, thus resulting in decreased scarring. In effect the extracellular matrix functions as a reservoir for regulatory proteins until they are needed for mediating healing, anti inflammation and anti scarring. Similarly, the promotion of epithelialization likely is a function of the extracellular matrix and basement membrane as it produces growth factors, acts a substrate for growth and facilitates migration, adhesion, and cellular differentiation of epithelial cells.

Clearly, five minutes is not enough time to discuss all of the functions of the embryonic membrane in vivo and in transplant recipients. My written presentation contains a more detailed analysis with citations, but even that is not comprehensive. Rather, this overview is intended

to demonstrate that scientifically and biologically the functions and characteristics of amnion and chorion are multiple, not singular, and are both structural and non structural. More importantly, these functions are derived from the inherent biological properties of these membranes, the biological properties and functions of the amnion and chorion as modified and processed into tissue grafts products is derived from the biological properties and functions of native amnion and chorion.

Thank you. (Applause)

DR. WITTEN: Thank you. Our next speaker is Harold Brem.

DR. BREM: Good morning. My name is Harold Brem; I'm a general surgeon, Professor of Surgery at the Stonybrook University School of Medicine, Chief of the Division of Wound Healing and Regenerative Medicine at Winthrop University Hospital.

My team of physicians and surgeons perform over 1000 operations per year with

regenerative medicine, including 24/7, and over the last 18 years we've treated over 50,000 new patients, most of them like the case reports you've heard over the last two days, very vulnerable patients who are coming to us at the end for treatment, limb salvage, and the other terrible destruction that happens with the (inaudible) and so forth.

We also have a robust research laboratory, a clinical research program and have been funded by (inaudible) for the last 16 years.

I really appreciate the opportunity to comment. I would like to begin by applauding you for the issuance of these guidelines, which will bring much needed clarity to the entire field and thereby create certainty for us clinicians that the human cell and tissue based products that we use to treat our patients are safe and effective. The tiered risk based approach embodied in the existing regulatory framework is entirely adequate. When compiled with, for determining whether a product is appropriate for regulation

solely under Section 361 pathway, rather than needing premarket the demonstration of the product safety and effectiveness. However, today there is a vast array of new allograft derived products in the market without proven efficacy. Many of these products make a range of therapeutic treatment claims that involve complex cellular and biochemical interactions with the body that for any other product type would require FDA pre market review commensurate with the risk level. It is clear that allograft products have made claims about their cellular activity should deregulate it as biologics, and I urge you to do so.

Arguments in favor of the status quo which allow allograft distributors to evade the need to generate valid level one evidence that has been subjected to rigorous peer and regulatory review by the FDA, the patients at risk do not advance care. Contrary to the assertions of many in the allograft industry is not the case in imposing premarket review requirements would delay

or prevent the entry of important therapies. Investment funding is well available for promising biotechnology and alternative pathways currently exist for addressing unmet clinical needs through accelerated review. Furthermore, the FDA should be perceived as a partner to our patients and to physicians, and industry, in working with them to bring safe and efficacious and high quality products that the patients richly deserve.

The remainder of my comments address minimal manipulation and homologous use draft guidelines specifically. In order to ensure that the tiered risk based framework outline in 21 CFR 127.1 functions properly there must be clearly defined boundaries, which these guidelines do accomplish for the most part. Regulating cells and tissues based on their primary or main effect not only provide administrative efficiency, but provides certainty to the regulated industry. This principle is well established and consistent with FDA's approach for its regulation to biologics, drugs, and medical devices and is

entirely appropriate for human cell and tissue based products.

The distinction contained in both the minimal manipulation and homologous use guideline documents between structural and non structural tissue and cells is long standing and exceptionally entirely appropriate. FDA has previously explained its reasoning for this distinction, which is that structural tissues raise fewer safety concerns beyond adverse local effects.

Again, I urge you to articulate more fully the rationale and to implement these guidelines.

With respect to tissues that serve both structural and non structural functions, I believe the approach taken in the minimal manipulation guidance document, referring to, "The main function of human cells or tissue product in the donor" is appropriate and should be preserved with the documents are finalized.

I join all the other commentators who

urge FDA to move swiftly to finalize these guidelines. Imposing regulatory order in the wound healing space is critical to protecting a particularly vulnerable, chronically ill patient population who deserve these therapies that are proven through valid scientific evidence.

Thank you very much. (Applause)

DR. WITTEN: Thank you. Our next speaker is Julie Cerrone.

MS. CERRONE: Hello. My name is Julie Cerrone, I'm years old, and I'm from Pittsburgh, Pennsylvania and I hope

that I can get through this without totally breaking down and crying, because it's amazing that I'm actually standing here unassisted wearing cute wedges, if I may add, because mobility and getting out of bed and walking up the stairs was something that I took for granted, something that I did every day, but I had it taken away from me and I wasn't sure that I was going to get it back.

When I was in fifth grade I had my first

knee surgery and in 2012 I faced my fourth and fifth knee surgery. And as I was going through this I kept having more and more knee pain and my doctor kept saying, oh you're fine, nothing is wrong with you, and I knew there was something wrong. There was something wrong. It was to the point where I couldn't stop shaking. I was in control of me shaking. You know, when you talk about a pain scale of 1-10, this was 1000. And I will always remember December 17, 2012 when my doctor walked into the examination room and said, well, part of your femur bone is dead, it's called avascular necrosis. I know what it is, I've seen it before, but I don't really know what to do with you. I don't know how to treat it and I really don't know where to send you. He continued to say that you probably will need to get a knee replacement. You could probably get two in your life and good luck, and sent us on our way.

I'm a pretty positive person, but I started doing the math in my head and I thought, well, crap, I'm going to be 60, young age of 60,

and am I going to be able to play with my family, am I going to be able to walk, what am I going to do. So I really relied on my family and friends and patient leaders on line to try to figure out the story because I had nowhere to turn to. I lost count at about 28-29 health practitioners that I went to looking for an answer. Top bone specialists, top orthopedics. I would walk in there and they'd all say well, I know what avascular necrosis is. If you were older I'd give you a knee replacement, but because I also had -- well, I have psoriatic arthritis and at the time I had complex regional pain syndrome, nobody wanted to touch me with a 10 foot pole. You know, I'd walk into these top, top, top leading doctors with such hope and I'd leave just completely defeated with my family in tears because no one would give me a solution.

I found my own solution though and that was a Regenexx stem cell procedure. And in March 2015 I went and had the procedure done on my left femur bone. Three months out I was off all of the

pain meds that I had been living on three to four times a day for three years at that point. Six months out, forty percent of my bone had regenerated and I was able to get off the crutches that I was on for 3 1/2 years. And a year out 60 percent of my bone had regenerated.

Today I stand here unassisted a year and a half out and really the only barriers that I face now in life are mental that I think I can't do things, I think I can't walk, I think I can't do physical things, but I can because my bone has solidified in a way that it's not going to crumble. And I think back to all those top doctors that I went to and the best advice that I go was, "to walk on crutches for the next

years until your bone completely crumbles and then get a knee replacement". And that was just absolutely unacceptable to me. There are so many different ways to treat avascular necrosis and they all have low outcomes. And I started talking about stem cells and trying to figure out if that was an option for me and I

had doctors say well, we have these prefilled placenta syringes, why don't we try that. And, you know, with my autoimmunity and with no long-term studies of those things I was very, very hesitant. So I am so thankful and grateful to all of the powers that be that led me to the stem cell procedure that I had. I was able to tap into my innate healing ability which each of us have. You know, given half a chance our bodies will heal themselves by ourselves. And we need to give patients that chance. So doing the studies, making these procedures available to patients.

Today I just wanted to share my brief highlight of a story for you and, you know, let's do this together, let's make this readily available for all patients. I never, ever wish AVN on my worst enemy and I sure hope that you or your family never has to go through this. But drafting regulations that allow people to tap into that innate ability, you know we can solve these problems for all of these patients.

So thank you very much. (Applause)

DR. WITTEN: Thank you. Our next speaker is Georgianna Crocker. Is she here?

MS. CROCKER: I'm just waiting for my slides?

DR. WITTEN: What?

MS. CROCKER: I had some slides.

DR. WITTEN: Oh. I'm sorry, did I skip -- no, that -- yeah, that's right. Okay. Okay, good.

MS. CROCKER: Good morning. My name is Georgianna Crocker; I'm from Austin, Texas. I just want to say I'm a patient here. I'm advocating for myself today and to share my story with you.

Thank you for allowing me this opportunity to speak with you directly about the regulation of adult stem cell treatment and how this treatment has given me my health and my life back. I am a rheumatoid arthritis patient who is currently in remission because of stem cell therapy one and a half years ago. I am a passionate patient advocate for adipose autologous

stem cell therapy, or rather using my own fat tissue, and keeping this therapy available and increasing access for patients like myself who have failed other conventional and non conventional therapies for their disease. I'm also a professional pharmaceutical rep who has been involved with the marketing and sales in medicine, including biologics, since 1999. I believe in the power of medicine and I highly respect the FDA for their active role in keeping patients such as myself safe.

Why am I here today? I'm here today to request that you, the FDA, continue to allow my stem cell therapy using my own fat cells, that this will be a choice made between me, myself, and my healthcare provider. I'm here to address any concerns you have regarding the safety and efficacy of using my own stem cells by showing you my first hand experience of this life changing therapy.

As you know with nearly all medicines and biologics, there is a percentage of patients

who do not meet the primary end point remission. And stem cell therapy is a treatment that simply cannot be ignored as a viable and safe treatment for usually about half of patients who don't meet that end point in their studies.

A little bit about my story is I was diagnosed in 2006 with RA. I immediately sought out treatment from the best rheumatologists and healthcare providers available in Los Angeles. Progressive pills, steroids, injectable biologics, and infusible biologics were all on board in a short time. They all had some success over the years and I'm grateful for that. However, over the years they failed. By the end of 2014 my RA medication stopped working, my inflammation markers were continuing to climb, and I was incredibly sick and in pain and suffering, despite being compliant with conventional and non conventional therapies.

In January of 2015 I was extremely ill and out of desperation I started doing on line research for drug studies. However, I was too ill

and I had failed too many other drugs to qualify. It was actually on antiage.gov that I learned about stem cell therapy and the promise of help. But unfortunately it was not main stream or approved.

After researching ADSC and clinics offering this type of therapy, throughout the world I looked, I chose to have treatment in the United States because I felt that it was safer than traveling abroad, and with the clean safety profile of using my own fat cells I had little to lose. At this point my hands and feet were swollen, exhaustion was overwhelming, I could not sleep, I had trouble staying awake, and you can imagine how this affected my quality of life and my family.

In February of 2015 I had ADSC therapy with StemGenex in California. Within 48 hours after my therapy the pain in my hip was gone. Within a week I could see my knuckles for the first time in years, and over the next three months my health improved so much I was able to

get off conventional medicine. And, to date, I am still pain free and RA medicine free a year and a half later. Without stem cell therapy my life would literally be a different story. I believe I'd be on disability instead of working and contributing and being able to support my family. My health is great and I actually performed in a half marathon this July. I'm sorry, I get emotional.

In the following slides you will see a short snapshot of some of my labs. Coming from a little bit of a science background, at least in my profession, I wanted to see, is this placebo, is this snake oil, and indeed in my case and in many cases, it is not. I've also submitted my full labs along with my presentation as time constraints require I can't go through it all.

This is a snapshot of my CRP, or C-reactive protein, a marker of inflammation. You'll see throughout 2014 all of the sudden my inflammation started climbing, during injectable steroids, oral steroids, and monthly biologic

infusions, and many other medicines. Six weeks pre therapy I had my labs done. My CRP was 1.9, normal is 1. I had my CRP done again 1 week post therapy and it had already dropped to 1.2. And as you can see throughout this slide, at different points over the last year I've had these labs done and actually I'm so low that I'm actually off the graph now of less than 0.3. This is just another way to look at those numbers.

This is my sed rate, another marker of inflammation. Again you can see in 2014 my body just went out of whack; it was not being controlled at all. Normal is 20. Six weeks prior I was 25. One week post therapy, 22, and it has continued to fall over the last year and a half, well within normal range. It's just another way to look.

My white blood cell count was above normal and it was cut on half in one week post therapy and has remained normal.

In conclusion I ask that you strengthen my rights as a patient to be treated with my own

stem cells and to accelerate this availability of treatment that is safe and effective, and to please not classify my own cells as a drug. They are my own cells and I ask that you respectfully treat them that way.

Thank you for your time very much.

(Applause)

DR. WITTEN: Thank you. The next speaker is Fiona Cunningham.

MS. CUNNINGHAM: Thank you very much. It's an honor and a privilege to be able to speak today. I'm here as a mother of a patient who has been incredibly sick since the day she was born. Her main diagnosis was systemic juvenile idiopathic arthritis and dysautonomia among a myriad of other very severe autoimmune and life threatening problems.

Her entire life has been filled with pain and hospitalizations. My identical twin sister had the exact disease and she died prematurely from this disease, so I have watched two people who I love from the bottom of my heart

be brutalized by their autoimmune systems. There's no other word than just say brutalized.

Due to the aggressive nature of my daughter's disease, when she was a baby we moved to Houston, Texas to be near a world class medical center. Throughout her life she's had world class medical care. She's been the subject of many peer reviewed medical papers because of the aggressive nature of her disease, and so there is mountains of very sophisticated bio and genetic data on her case. She almost died many, many times and she was so sick her world class care in Houston also sought out the care here at the NIH. And so it's very strange being back here when -- I stayed at the Children's Inn and she was actually treated here at the NIH, so that shows how sick she was.

By the age of 22 her body couldn't stand it any longer. The side effects of the drugs and the progression of the disease had gotten to the point where she was dying. She'd literally run out of every traditional treatment, nontraditional treatment, experimental treatment that was

available in the United States. She had become a skeletal figure, was bed bound, in severe pain. And even Sarah knew her time was up, she said, this is it, mom. And then we heard about high, high dose autologous mesenchymal stem cells taken from a one-time adipose fat extraction. My Sarah is -- her name is Sarah, she's going to be speaking today -- she is highly allergic to most drugs. If you look at her allergy list, it's a laundry list of drugs. And these are severe reactions where she gets anaphylaxis, looks like elephant man. And also her body doesn't react well to biologic products. So she has to pre-meded up to the hilt for any biologic product. We also understood to combat the aggressive nature of her disease that she had to have extremely high doses of incredibly pure doses of her own mesenchymal stem cells.

So these were taken from a one-time fat extraction. She was too weak for multiple extractions, we knew that. Just the one-time fat extraction put her into a cytokine storm. We

deliberately sought out the FDA regulated biotechnology company called Celltex Therapeutics to bank, expand, and culture Sarah's stem cells in their CGMP laboratory that is regulated and they look at all the safety margins and everything and really adhere closely to everything that the FDA wants, and we thank you for that and that is one of our biggest reasons it has to be CGMP lab, it had to have safety measures in place.

People often worry that stem cells are not safe. And firstly, it's important to remember that Sarah's stem cells were manufactured in a FDA CGMP laboratory that's regulated with a company that has proven protocols and safety records. Secondly, Sarah's overactive immune system that reacts to everything has readily accepted 5.25 billion of her own stem cells over 22 infusions over the space of almost 2 years. She has not had one adverse reaction. It's like her body was saying, thank you. Not one.

She's not the only one that has gone through this. Sarah followed a little six year

old boy called Tucker Beau Hyatt, and his mother gave me permission to talk about him today. He's had the same severe autoimmune diseases. Because he's younger he wasn't as progressed. But his parents are fully aware of the path that lay ahead of him. He's now an eight year old --

DR. WITTEN: Excuse me. We really appreciate your comments, but you'll have to wrap up your remarks so we can move on to the next speaker.

MS. CUNNINGHAM: Tucker Beau and Sarah have survived because of their high dose stem cells without any, any reaction whatsoever. What saddens me is that they had to get on a plane and fly to Mexico to receive their own stem cells that had been manufactured in the United States.

In closing, could I ask that we look at Celltex and all from all the research they've been the leaders in regenerative medicine from everything that we could find. Look at the scientific data that has been compiled on Sarah, Tucker Beau, and Celltex, and I ask you to

seriously consider them as the industry model. I mean they saved my child's life, they saved Tucker Beau's life.

Thank you. (Applause)

DR. WITTEN: Thank you. The next speaker is Roxana Daftarian.

MS. DAFTARIAN: Good morning. My name is Roxana Daftarian and I have MS. First of all, I'd like to thank the FDA for the opportunity to speak about the draft guidances relating to the regulation of stem cells.

I'm 55 years old and no MS drug has worked for me. I was diagnosed in 2002 and for two years I was on nothing and I was perfectly fine. At the insistence of my neurologist I went on Avonex and a year later my legs started acting up and there was extreme weakness and I could barely walk. I changed neurologists and the new one told me that I was allergic to all interferons. I tried Tysabri for six months and after six months I showed antibodies to Tysabri as well. So I can't do that either. So basically

I'm allergic to most MS drugs and I've been on nothing for the past I would say six-seven years.

I did some research on line because my legs were getting weaker and weaker. After coming up with this center in Germany my husband and I travelled to Germany for stem cell treatment and the results were amazing. I could -- I mean my leg immediately improved, my foot drop was gone, my -- the tremors in my body were gone and most of my symptoms just disappeared.

When I came back a few years passed by and I did more research because I could not take any drugs, and I found this place in California for stem cell. So I decided to go there in 2013. They used my adipose stem cells. So I did it and the results were again amazing. I've done stem cell five times all together, so I would consider myself among the lucky few. The results are just simply no side effects, safe, and very, very good. I would recommend stem cells for anyone who has MS. I cannot tolerate drugs. Because this one has no side effects whatsoever, it's your own stem

cells.

I recently had two bouts of pneumonia in the past three years. I recovered extremely well. Literally, after one week and I think it's because of the stem cell because my body just rebounced back so fast from everything.

I had a surgery and -- there's a nerve in the base of my skull that they had to work on and I did the surgery and everything was fine after one week so I contributed all these improvements to the stem cells that I have been doing over the past few years and I ask the FDA to please consider approving my own -- one's own stem cells for treatment of diseases like MS, Parkinson's, rheumatoid arthritis, all these things and that's it. Thank you very much.

(Applause)

DR. WITTEN: Thank you. Our next speaker is Rahul Desai.

DR. DESAI: Good morning, thank you for having me speak today. We will have some slides. I just wanted to let you know, I am a

musculoskeletal radiologist, interventional changed, allopathic background, Md, grew up in Ohio, trained at Washington University and developed a pain practice in Portland, Oregon.

Today, what I am going to be speaking about are the interventions that we are using for pain management so joint and spine and soft tissues.

Right now, and I'll give you a little bit of background how I came into this. I had a very standard pain practice, interventional, using a lot of cortisone and other modalities. It was very frustrating seeing patients come in. We don't -- I don't use any narcotics and we want to get these patients healthy and it was very frustrating to see them come back over and over again and the situation worsening with their joint disease.

Progressive arthritis, worsening disc herniations. We'd give them more steroids, they would have side effects and gain weight and they weren't getting better. And so I was looking for

solutions about seven or eight years ago and I heard about the date.

And I am a -- out of any type of doctor out there, I am a radiologist, I am pretty black and white, I want to see that there is something going on. I was a skeptic and it took me a long time, even after doing these therapies to really believe what I was seeing.

We started to do these therapies on ligaments and tendons so I vetted it out. It looked like these platelets had been done in veterinary medicine, orthodontics, it would seem like it was a safe tool. We tried -- we started using them in soft tissue injuries, rotator cuff, Achilles, those types of injuries and patients were coming back after a few weeks saying: "Doc, I feel better. I'm healed. " And it was shocking to me so with the benefit of my company that I was working for, we scanned a lot of patients and they were -- the images showed that the situation was better. Over the past -- and there were paradigm shifting so I'd never seen that -- I am going to

skip through some of these but I had never seen that before with any other intervention that it was a change of paradigm, that you could actually repair tissue with a single injection and no side effect profile and this happened over and over and I've treated several thousand patients over the past eight years using this.

As we started to go through different tissues, what I am going to focus now, especially since it's a huge issue right now in our country, is low back pain and degenerative disc disease.

We are seeing that this actually works for that and now we are using more powerful tools, such as bone marrow adipose grafts. We don't digest the cells and PRP and we're doing those in the epidural space and on discs.

This was the first case I ever did on a patient who came to me and he came specifically for sciatica. He'd had other therapies and on this MRI, you can see here the red circle on the tope is the oldest image. He had a large extruded fragment in the disc space and the nerve is being

squashed and he's having low back pain and sciatica.

He came in and wanted PRP. I said "I am going to give you steroids. The standard of care, I am a little bit afraid to go down that path" even though we do blood patches and put blood in the epidural space all the time.

We did a couple of steroid injections. He had a couple of days of release and we knew the pain was coming from this. I gave him -- he came back and said: "You promised me, doc, do the PRP. " So we went ahead and we did the platelets. A week later he called me back and said: "Doc, all my sciatica is gone. I have a 1 out of 10 pain in the back. " I said: "Come back and we'll put you on the scanner, let's see what's happening and so now we have hundreds of these types of studies on imaging and we're seeing the same thing with larger disc herniations. That was just epidural.

Now we are actually putting it in the disc and we're seeing this with a patient four years old. Two young kids, chronic progressive

low back pain, debilitating. Her choice was fusion.

She had had steroid injections, she had had physical therapy, she was on narcotics and she went to the surgeon and we heard the same story, that they are going to do fusion procedure on this patient and I think we have to be able to allow these types of therapies, which are minimally invasive to help them.

This patient came back after three weeks. Her pain started to diminish. This is a six month before and after image and you can see these large herniations, extrusion, lifting of the tubal ligament. This is all gone. This was -- you can see the nerves being compressed.

This is -- after you see the small -- we are seeing these morphological changes over and over. I just hired as -- and I understand that we need guidelines and we need research and so I've just hired, even though we're just a small practice, hired a PhD to help us do the research and show this is another clear example of what's

happening with this material, an extruded fragment pressing on the nerve root. This was gone after 12 weeks, after one injection and these patients; they're not showing up acute because you could say: "That could go away. "

These are patients that have had this long term, with other interventions and it's not going away and then we do this simple intervention and it's helping and so what I'd like to propose for the FDA to at least consider is to use autologous material -- homologous material. This is not -- we don't think the cells are actually changing and creating new material, but they are affecting a change long term and allowing for the healing process. Thank you for your time.

DR. WITTEN: Thank you.

(Applause)

DR. WITTEN: Thank you, the next speaker is Yoelma Eid Sandoval. Is she here? Ryan Fitzgerald? Okay, I am just going to ask for the other two speakers that weren't here earlier just to check and see if they are here, Waldo Acebo?

Kara Couch? Okay, so I think this -- we're -- we've completed the speakers from this morning's session and we are going to take a break for lunch.

Since we are a bit early for the lunch break, I'd like to suggest that we resume early so I am going to propose that we resume at 1:15. So can everyone be back in their seats at 1:15?

(Recess)

DR. WITTEN: I'd like to start with Timothy Freeman?

MR. FREEMAN: Can I start now? Okay. My name is Tim Freeman and 40 months ago, in the prime of my life, I was diagnosed with early onset Parkinson's disease. Today, I am here today to address concerns related to the safe and effective use of both allograft and autograft stem cells as treatment options for many medical conditions.

I am in a unique position. More unique, I am sure, than any of your presenters for these two days. I have seen firsthand the effects of allograft stem cells with corticocancellous bone

and the robust fusions that we've got in spine surgery, from products such as MTFS Trinity. I am also the recipient of adipose derived mesenchymal stem cell autograft for the treatment of my Parkinson's Disease.

I am asking the FDA to not over regulate the usage of stem cell products and to allow my chosen medical professional to have the ability to treat me as they and I see fit. In May 2013, I was diagnosed. I knew before I even went to the neurologist because I had seen the advent and the subsequent struggles that my mother experienced with Parkinson's. At that time, there was no regenerative medicine and there was no stem cell treatment to consider.

There were only the toxic chemical drugs to take and within a five year span, my beautiful, healthy, wonderful mother was gone. Based on that, I made the commitment, after my diagnosis, that my life was not going to be relegated to infirmity before death and at the age of 49, with an incredibly supportive wife and family, I am,

and will continue to seek out the best treatments for me, even if it means going overseas.

I've been a firsthand witness to the toxic side effects of the current medications that are available for Parkinson's and I would prefer to never have to take them. The side effects can be as frustrating and debilitating as the disease itself and how sad is it that the best drug on the market today was approved in 1967.

Let that sink in. Let it sink in. We have been treating this awful disease with the same medicine for 50 years. In reality, L-DOPA isn't really a treatment. It's simply a masking agent that over time loses its effectiveness to finally not working at all.

I can only believe that the pharmaceutical companies haven't been interested in developing new treatments because our numbers haven't been great enough or it was considered a disease of old people.

There are new faces of PD now and it's mine, and it's my friend Jimmy in Chicago, who has

been treated with intrathecal transplant of allograft stem cells.

Before his treatment six years ago, Jimmy was on a walker at the age of 33. Post treatment, Jimmy has run 75 half marathons, six full marathons and countless 10Ks. Now with the advocacy of the Michael J. Fox foundation and the dollars and notoriety that they bring, we finally have significant critical research being done. Without Michael, I'd hate to think where we would be in traditional medicine and research.

I investigated and explored many options before I made my decision to move forward with my stem cell treatment. As a result of my treatment, I've had much more energy whereas I had been taking naps, long naps in the middle of the afternoon every day, I now can work full days and I have not had an afternoon nap since my first treatment.

Every time that I would sit down to watch a game or a show on TV, I was falling asleep. Going to see a movie was worthless

because I would miss half of it from falling asleep. Now I can actually watch a movie and not fall asleep. My focus has been clearer and sharper, I am interested in what I am doing and I am back to being social again.

Overall, I just feel better. My sleep habits have improved greatly and my bouts of night terrors and acting out dreams have diminished greatly. I still have tremors and I was never promised that my treatments would cure me.

The best part of it, I've had no side effects. As I look at the landscape that stem uses and the diseases they treat, I see the need for balancing safety and adoption of use. The primary function of the FDA is to ensure the safety of products and technologies are coming to the marketplace. Placental, umbilical, amniotic stem cells have proven safe; therefore that hurdle has been crossed.

Across the world, most notably Europe and Japan, others appear to be moving at light speed and utilizing stem cells to treat diseases

such as Parkinson's and MS. I have never been promised a cure by anyone. I have paid for these out of my own wallet and had they not been effective, I would have not gone back for a second and third treatment.

As a result of my experience with the use of different stem cells and their uses, I am asking the FDA to not put shackles on innovation. I ask that you help the scientific community by accelerating the use of these safe and effective stem cell treatments to all Americans.

In conclusion, if you were me, or your wife, or your husband, your son or daughter, would you not go to the ends of the earth to ensure that you had one more day, one more year, one more decade, one more healthy life to spend with them? Regenerative medicine, in some form or fashion, is going to be the answer in treating and eventually curing these awful debilitating neurological disorders.

Please do not impede this progress. Thank you again for the opportunity to speak on

behalf of patients across the country about the draft guidances relating to the regulation of adult stem cell treatment, thank you.

(Applause)

DR. WITTEN: Thank you. Is Brian Gates here? Okay, next is Marie Gehling.

MS. GEHLING: Good afternoon, my name is Marie Louise Gehling and I am a nurse practitioner and a certified wound ostomy continence nurse at the regional medical center in Orangeburg, South Carolina. I have been a registered nurse for 32 years.

I founded the wound center at the regional medical center in 1992 after seeing far too many lower extremity amputations in patients both with diabetes and vascular disease and after taking care of many patients suffering from the stress of having a chronic wound that wouldn't heal and little available resources.

Wound care has changed a lot since the early 90s and we as providers have many more resources to manage patients with chronic wounds.

We have a viable limbs salvage program at our hospital because of both advancements in science and technology and therefore have fewer lower extremity amputations than in the past.

These advances in science and technology have led to an explosion in the growth in the wound care industry. Many times, this growth has been at the expense of true scientific evidence.

One area of ongoing concern has been about the lack of rigorous evidence supporting therapeutic claims for a growing number of allograft derived products that are promoted as healing agents.

The claims made of wound healing, reduction in inflammation and reduction in scarring are made by various product manufacturers. These products have been brought to market under section 361 of the public health and service act, which only concerns the transmission of infectious diseases when additional concerns for safety and efficacy are not addressed.

In order to promote wound healing, the product would have had to have gone through the much more rigorous PMA or BLA approval. Despite this, manufacturers are marking products under section 361 pathway without any pre-market review and then making claims that are not supported by FDA trials as is required under the premarket approval process.

The current reimbursement by centers for Medicare services increases the confusion about proper use and provides a good example of the confusion created as a result of lack of regulatory clarity for industry around the meanings of homologous use and minimal manipulation. When CMS bundled the payments for tissue products, this allowed products with FDA reviewed clinical trials to be lumped in with products that have limited level one evidence.

As a result of this, reimbursement methodology, products without FDA reviewed safety and efficacy data adopted claims from the products approved through the premarket process. They

stated: "We are just like product A" and the company who had correctly achieved the premarket approval, this is very problematic.

If providers are not educated on the difference or the standards of the products regulated under section 351 in section 361.

When manufacturers realized they could get payment without FDA approval, the marketplace for human cellular products and tissue products erupted and continues to grow exponentially. This unregulated growth in the industry, not supported by valid scientific evidence or rigorous research has taken guidance documents that were clear in their verbiage and manipulated them to meet their own needs, thus leading to false or misleading claims of wound healing for which the FDA has very defined specific criteria.

If a manufacturer wants to cite a therapeutic claim for healing, or reducing inflammation, then it must be supported through rigorous human trials.

The allowance of payment for a product

does not lend legitimacy to its claims, however it does lend to confusion. Why would the CMS allow the same payment for a product that is not an FDA approved therapy when there are safe and proven therapies backed by sound FDA reviewed evidence and that meet the FDA's high standards for safety, efficacy and quality.

Our patients are entitled to the highest quality care available. They are entitled to know that their care providers are not being misled as to the nature of or the risk associated with these therapeutic products they are receiving. They are entitled to rely upon the natural assumption that we all make that someone other than the companies who stand to profit from the product, or the sale of that particular therapy has reviewed the data to support the therapeutic claim being made for that product and has determined that that data is robust and derived from a well designed, well executed clinical trial and that they are relevant to the particular claim being made for healing.

Unfortunately, today, patients are being

lied to by omission. The system is failing them because in fact, many of the products being marketed as advanced wound healing biotherapies have never been reviewed on a premarket basis and neither is there any oversight of their claims in a post market basis and in fact, there is virtually no adverse advent reporting for these products.

To make matters worse, this reality is beginning to play out in other therapeutic areas as well. For these reasons, I urge the FDA to finalize the guidance documents under discussion toady with all possible haste in order to strengthen the boundaries between the properly regulated and solely -- those products properly regulated under 361 and 351 and I would like to thank you for your time and attention.

(Applause)

DR. WITTEN: Thank you. Our next speaker is Ted Gradel.

MR. GRADEL: Hello and thank you for the opportunity to speak today. My health issues are

relatively modest compared with so many of the fine presenters today so I will gloss over those rather quickly.

I was diagnosed with moderate osteoarthritis in both knees four years ago at age 48 and told I had no other options other than to endure the pain and eventually have knee replacement surgery.

I sought out the alternative, stem cell therapy and the results have been fantastic. When you deal with chronic pain, even though mine was modest, on a regular basis, it's quite liberating to wake up pain free every day. Now, four years later, I have been diagnosed with moderate to severe osteo in my left hip and two different orthopedic surgeons have told me I have no options other than endure the pain and eventually get hip replacement surgery.

I am very thankful that I know about the procedure I already had. I am very thankful that I have the option of stem cell therapy right now and I plan to schedule a procedure soon.

A couple of things I am having a hard time understanding, and I do have a different perspective than that last speaker and I respect her opinion. I respect how difficult this is to process but I am having a hard time understanding and talking about just the autologous stem cells, my own stem cells. How is this being considered regulated as a drug?

When I look at that little vial, the little sliver of SVF, stromal vascular fraction that is sitting at the bottom of that test tube, those came out of my body and those are my cells. I am having a hard time understanding how -- I don't really care if the lab technician added an enzyme or if they have been manipulated either minimally or maximally, I feel like I should have the right to have those cells injected back into my own body, without having to deal with government regulations and extensive testing or anything like that.

That decision should rest between me and my physician. If you surveyed the average U.S.

citizen and asked whether they should be allowed access to their own blood, tissue or cells or whether they would prefer the FDA restrict that access, I have a very strong opinion that the vast majority would say that decision should be theirs and their physician's.

The other thing I am confused on is it just seems that there are so many people who are again, very smart, educated, experienced people, PhDs, Mds, that are so violently opposed to what is going on and it's almost like they take any success stories, which we have heard so many of today and they are awesome stories. Julie and Georgianna and Shelley -- all the people that have talked about how they have benefited, it just seems like so many people want to downplay those and say: "Well that's just anecdotal evidence and they didn't have proper testing. "

Whereas you take a couple of adverse, negative adverse events and these critics want to blow those up, highlight them conspicuously and hold them up as a reason to disallow these

procedures for everyone. It doesn't make sense to me as an average, non-medical, layperson.

I ask that you -- there will be negative outcomes and those are extremely unfortunate when they happen, absolutely but we must learn from those rather than running from those. I ask that you consider how many thousands of U.S. citizens will be negatively impacted if these procedures are restricted in big ways.

People suffering from chronic debilitating conditions -- as mentioned by so many speakers, the demand is there and other countries have approved these procedures. If we force thousands of patients to look overseas, it will likely be more costly and less safe. Many thousands more won't be able to afford those procedures in traveling and so they'll be forced to live with debilitating conditions when they might otherwise have had an option.

I truly believe that these stem cell therapies have the ability to positively impact so many lives and I ask that you keep that decision

making ability where it belongs, in the hands of the individual patient and their physicians. Thank you.

(Applause)

DR. WITTEN: Thank you. Is Scott Graham here? Our next speaker is Sarah Hughes.

MS. HUGHES: Good afternoon. My name is Sarah Hughes. I am here today on behalf of 117 million Americans who are chronically ill. That is a little over one third of the United States population suffering from chronic disease according to the CDC.

Did you know that seven of the top ten causes of death in the United States are chronic diseases, with arthritis being the most common cause of disability in America.

I am turning 25 years old in a few weeks and I have lived with systemic, severe systemic juvenile idiopathic arthritis my entire life and if not for the help of high dose autologous mesenchymal stem cell therapy, I would not be here today.

My journey with stem cells started in 2014 when I was 22 years old. Up until that point, I had lived most of my life in critical care and my doctors said my time was running out. I tried all traditional treatments but I was met with limited or no success.

Using one of the least invasive stem cell therapies known in the United States, I have experienced a transformation that my doctors call a medical breakthrough.

My doctors have reduced the number of prescription drugs I was taking from 23 down to 8, at lowered doses. I can eat again and absorb the nutrients. I am not in constant pain and I haven't needed chemotherapy or been immune suppressed since my first stem cell infusion in November of 2014. Due to the aggressive nature of my disease, I was treated and studied here at the National Institute of Health so it is a privilege and with a lot of emotion that I stand here today in fairly good health to share my testimony.

Because my own stem cells are considered

to be a drug, I had to leave the United States to have adult stem cell therapy from an FDA regulated biotechnology company based in Houston, Texas called Celltex Therapeutics.

I was running out of time but I was willing to put my life at risk to get on an airplane. My quality of life had become so dismal, even one small improvement from my own stem cell would have been enough for me.

What happened in the days, weeks, and years following my first infusion has changed my outlook. It's hard to believe in my sick body, I had a wealth of healthy adult stem cells with the ability to so significantly improve my quality of life. Before stem cell therapy, I wasn't planning my future because simply, I didn't have one.

Now I wake up every day and I am grateful but overwhelmed thinking about all of the choices I have now that I didn't have before. I also think about the millions of Americans -- millions of people in this country who are still living as I was, a shell of a human being, dealing

with constant pain and unable to think about tomorrow.

It's sad knowing the people who could benefit most from adult stem cell therapy are probably too sick to get on an airplane so I ask you this, if we consider American to be the greatest country in the world, why are we making it so hard for sick people to get better? Why do the laws call our stem cells a drug?

Regulation states that if our stem cells are expanded in large numbers through self-culturing, then they are drugs that have been more than minimally manipulated.

If you look at the science, my cells were not manipulated. Despite my overactive immune system, I have received over 5 billion of my own adult stem cells over the course of two years with no adverse effects.

The power of that many MSEs has been researched and documented over the past four and a half decades and yet America lags behind the rest of the world in the area of regenerative medicine.

Still, this experience has taught me the power of hope and my greatest hope now is that the FDA will work to shape a new path that will make stem cell therapy a reality.

I am alive today because my amazing team of doctors and many FDA approved drugs. I received my own stem cells cultured by a company whose product I knew to be safe because it is regulated by the FDA so I want to thank you.

In closing, I implore you to change the road we are on because we can do so much more with stem cell therapy. We have the innovators and the scientists in this country who can and will and are developing new and better drugs and therapies for Americans who are suffering and have no quality of life. We can do better than this, thank you.

(Applause)

DR. WITTEN: Thank you. Our next speaker is Scott James.

DR. JAMES: Good afternoon, my name is Scott James. I am a vascular surgeon at the Beth

Israel Deaconess Plymouth hospital in Massachusetts. I have been in practice for 14 years. I am Board certified in vascular surgery and general surgery. I commend the FDA on focusing on the need for greater clarity in the regulation of human cell and tissue products.

The need is particularly great with respect to human cell and tissue products intended as regenerative medicine therapies, an area that is driving new innovation and growth and holds much promise for patient treatments. In the future, and for meeting unmet medical needs, this is very important.

It is also an area in need of greater regulatory attention to ensure the safety of patients and to protect the public health.

Over the last ten years, an inadequately led regulated industry of large scale manufactured biological products has sprung up under the cover of a minimalist regulatory scheme originally designed to oversea, without undue regulatory interference, the distribution of traditional

organs and tissues for transplant.

The widespread marketing of section 361 allografts that do not meet the criteria of section 1271. 10 has been possible because the regulatory scheme leaves distributors of allograft products to make their own determinations as to whether their products qualify as section 361 human cell and tissue products. There are powerful financial incentives for these distributors to determine that their products can legally go to market under the section 361 pathway and few, if any incentives for them to determine that they require premarket review.

Not surprisingly, then, allograft distributors almost always conclude that no premarket review is necessary for their products. As a result, we see a disturbing number of product promoted to healthcare providers like us for uses that the FDA has never reviewed or approved up to including claims that these products are comparable or even superior to products that have faced rigorous FDA premarket review.

As a vascular surgeon, my own observations of these issues have occurred in the wound care, limb salvage and vascular surgical areas. In these areas, there are a large number of tissue products being marketed without robust evidence demonstrating their safety and effectiveness.

The marketing claims for these products have not appropriately substantiated and in some cases, they are also being marketed as novel applications.

The lack of premarket review over these products has sewn confusion on payers with the very real effect that the patient's access to therapies that are proven to be safe and effective has become much more limited.

The patients that we see in our practice have devastating conditions and the consequences of using treatments that are not backed by rigorous science can be disastrous. Our patients deserve to know that the therapies we give them have been proven to be both safe and effective.

It's that simple. Section 361 simply ensures the safety of cells and tissues from an infectious disease standpoint, that's really all it does but preventing tissues from transmitting disease is just the beginning of determining whether tissues or cells are safe and effective for indications that implicate complex biomechanical processes to achieve an intended therapeutic effect.

From the beginning, it was the FDA's intention that human cell tissue products intended for complex interactions that fall outside normal use for conventional tissue would place these products squarely in a higher risk category meaning that they would be subject to premarket scrutiny and greater post-market controls.

Allograft distributors who have taken advantage of the ability to self-designate their products as section 361, human cell tissue products, have thoroughly distorted the regulatory framework to the detriment of our patients.

In short, it's critical for the

wellbeing of all our patients that the AFDA take consistent and definitive actions to bring human cell products that are intended to interact with the body in complex ways, for example, in the manner of cell therapies be subjected to the same degree of regulatory scrutiny as other biologic products with more complex mechanisms of action.

The draft, manipulation and homologous use guidance documents are a critical first step in restoring the regulatory scheme and making it work as it was intended to work. For that reason, I join with the other commenters in urging the FDA to proceed with all possible speed in this approval. Thank you again for allowing me to give my comments.

(Applause)

DR. WITTEN: Thank you. Is Kristen King here? The next speaker is John Klimkiewicz.

DR. KLIMKIEWICZ: Good afternoon. Thanks for the opportunity to speak. I am a local orthopedic surgeon specializing in sports medicine. The topic will be the application of

musculoskeletal allografts within my sub-specialty of sports medicine.

The application of musculoskeletal allografts within sports medicine has increased dramatically over the course of the last decade. As formalization of the tissuemaking process has been verified and these tissues have been deemed safe, use within my field of sports medicine has increased dramatically. It's allowed application of procedures in a less invasive fashion and has also opened doors in aspects of sports medicine that were previously untreatable.

Today, we'll talk about the utilization of allograft tissue in ACL surgery, multi-ligament knee injuries, meniscal insufficiency and focal chondral defects or a low form of osteoarthritis.

In terms of ACL allograft reconstruction, ligamental stability has been shown to be similar to autograft tissue. The rehabilitation has been easier, thus allowing the application of this technique to an older population that previously was unavailable too.

Overall, in this population, it allows these individuals to be more active and results in an overall cost savings when looking at both future and current activity levels and further medical treatment.

It also allows the application of different principles to revision ACL reconstruction when autograft tissue is not available. Metanalysis studies have been done that have demonstrated equivalent results to autograft tissue and in certain populations, allograft can actually be shown to be superior than autograft for function and overall outcomes. Application of allograft surgery to multi-ligament knee injuries has allowed us, as surgeons, to address all aspects of the injury without going to the opposite leg for tissue in order to reconstruct the ligaments.

It's allowed us to improve the lives and functions of these patients dramatically. The success of allografts has also opened up treatments that previously were unavailable.

Meniscal allograft transportation was popularized in this country about two decades ago.

It's helpful to patients where the meniscus has been removed who are not yet arthritic but have pain. The traditional approach to a meniscal tear is the removal of the meniscus, which will only lead to arthritis in the future.

Some patients have pain despite the lack of arthritis and meniscal allograft transplantation has allowed us as surgeons to restore their activity and their way of life that previously was not able.

Biomechanics have stimulated this technique and have driven it and it's a technique that has been done with a lot of forethought both in the laboratory and in our medical clinics. Meniscus transplantation has been found to be successful in an intermediate period of five to ten years at

percent. Again, it allows us to address patients that

otherwise were untreatable until their

knees have become arthritic. Focal chondral defects is another area within sports medicine where allograft tissue has been instrumental in achieving patient success.

These lesions are either traumatic and they're degenerative and there is no intrinsic ability for the body to repair these.

There has been, up until this point, no consensus on treatment. Osteochondral allografts have been indicated for larger defects with the hope that the underlying bone will heal to allow the overlying cartilage to remain viable and functional.

Success rates for this procedure have been at 80 percent at the 10 year mark. In summary, as safety issues have been addressed through better tissue standards, allografts and sports medicine has allowed the expansion of current surgical techniques in a less invasive fashion that allow restoration of function and activity, increasing patient satisfaction and overall health.

Additionally, it has added to the treatment scenarios of sports medicine with currently few alternatives with the biologic potential to restore the biomechanics within the joint and potentially prevent further and future arthritic breakdown, thank you.

(Applause)

DR. WITTEN: Thank you. Our next speaker is Jeanne Loring.

MS. LORING: My name is Jeanne Loring. I am a stem cell researcher at the Scripps Research Institute in La Jolla, California. Today, I am speaking only for myself, not for my institution.

I want to speak about just one issue and that is having a scientific rationale for a cell therapy. Most of the speakers have been concerned with arguing that the FDA should have less oversight over the use of adipose tissue and amnion for transplantation.

Unfortunately, the lack of understanding or a deliberate ignorance of the regulations has

led to an increasing exploitation of desperate patients by incompetent clinics. The FDA needs to take action to improve regulation and I favor approval of the guidelines proposed. I do wish it would happen sooner.

I want to bring out the completely different idea about cell therapy because it hasn't been raised before. I want to make sure that people know about this. Adipose cell therapy is governed by that overused axiom, if the only tool you have is a hammer, you will treat everything as if it is a nail.

It isn't logical or scientific to assume that all disorders can be treated with a single type of cell. There is another approach, the use of pluripotent stem cells which is guided by defining the disease and deciding the cell therapy to treat it.

Pluripotent stem cells can be made by reprogramming any person's skin cells; they only exist in culture. They can make every single cell type in the body and they are currently being used

in clinical trials. They have been differentiated into retinal pigment cells to treat macular degeneration and to glial cells to treat spinal cord injury and into insulin producing pancreatic cells to treat type I diabetes.

Cell replacement therapy is designed to be, in this case, to be a onetime treatment. My group is working on cell therapy for Parkinson's disease. We've made induced pluripotent stem cells from individual Parkinson's disease patients. We have differentiated them into the precise neuronal type that is lost in the disease, neurons, and we are working toward obtaining FDA approval to transplant them back into the same patients but this approach, in which we rely on scientific evidence to design the tools to treat each disease is novel and currently has a complicated pathway to the clinic.

As Randy Mill said yesterday, there must be a way to redirect the FDA's unfortunately limited efforts so that they can efficiently identify the cell therapies that are safest and

most effective and apply their expertise to those as a priority.

I wish you well, and if you need any help from scientists, you should ask us. Thank you.

(Applause)

DR. WITTEN: Thank you. Our next speaker is Norman Marcus.

DR. MARCUS: Good afternoon. Thank you for inviting me to discuss growth factor treatment for non-surgical therapy of osteoarthritis of the knee.

I am an orthopedic surgeon in Springfield, Virginia specializing in cartilage repair. The demand for non-surgical treatment of the mild to moderate osteoarthritic knee is quite large and is based upon both elevated expectations of the baby boomer population as well as the well known poor results from some implant arhtroplasties. Frequently, patients with knee pain undergo knee arthroscopy and so called menisectomy and this population, even minimal

surgery can result in actually increasing symptoms, mainly because the true problem was not the meniscus but the articular cartilage.

Many MRI findings of so called menisal tears in this population are irrelevant and lead to unnecessary surgery. I have been using platelet rich plasma for the last seven years based upon variety of commercial and non-proprietary methods. There have been no complications in over 2,000 ejections. The technique is based upon a minimal phlebotomy and differential centrifugation predicated by cell counting both before and after purification so we know the dose.

The number of circulating platelets in our blood is highly variable, even at different times within the same patient and certainly between different patients at different times. By measuring the concentration and volume of platelets, a simple calculation yields the precise dose.

The procedures performed with non

proprietary lab equipment. The material values is leukocyte poor. Patient selection is critical and dose is important for this type of therapy to work. Five billion platelets over a six week period in mild to moderate osteoarthritis produces a 90 percent favorable outcome as judged by at least a 50 percent reduction in pain and a market increase in activity levels.

The injections are performed with ultrasonic guidance to ensure placement within the knee. The knee is then iced and other than nominal precautions, there is no therapy or post injection therapy or medication of any sort. The normal duration of a favorable response is about a year. This morning, a lady came in that I injected four year ago with a good result until recently. She wants a new series.

Some have been durable even longer. Should a second course of PRP be necessary, there is seldom any falloff in efficacy and the second course is again, usually effective for about a year.

Autologous platelet therapy, replete with growth factors is a very useful, safe, powerful and effective treatment for moderate osteoarthritis of the knee. Improvements could be made by dose standardization and further investigation into potentially useful subgroups of white cells, such as is being done in oncology.

These studies are unlikely to be performed by for profit enterprises as the commercial benefit would be very limited.

Patient selection is the key to achieving these results. Many people have been prematurely advised to have total knee surgery when in fact, injection therapy appears optimal for many years. It is a treatment, not a cure. We should all want that each patient who needs a total knee gets one and only one for his whole life.

One final word about amniotic preparations, the material from amniotic fluid arrives frozen from the tissue bank and I've used it in about 10 people in conjunction with PRP. It

has no shelf life. It is unclear whether it is of any benefit at the present time. The material does not come with a manifest, a cell count or a growth factor analysis.

The quality assurance process remains obscure even when you phone these companies to ask what it is. There is no dose response relationship and it's unclear whether growth factors are even present in these amniotic preparations. Appropriate labeling on allogenetic growth factors would seem to be indicated, such that we can all determine which combination of non-surgical methods achieves the most consistent results. Thank you very much.

(Applause)

DR. WITTEN: Thank you. Our next speaker is Brian Marr.

MR. MARR: Thank you. Thank you. I appreciate the opportunity to come before you all today. My wife is going to speak after me. I want to thank you for allowing -- I am going to talk to you a little bit from a different

perspective as more of a caregiver. My wife has primary progressive MS and we've been dealing with it for quite a while.

I have two great children but these diseases that we are hearing about today affect much more than just the victim themselves. It affects the family members, it affects our abilities.

Now we have gone through all the standard treatments that we can for primary progressive MS and there is very limited -- we have gotten on lots of medications.

All these medications had toxic effects on my wife and from going from one drug to a secondary drug to a third, to a fourth, to a fifth, each has some type of different issue that comes up a little bit later so the standard protocol by which we were using to try to fight her MS was just not working for us so after we had tried all that, we started researching out and seeing what could we do to benefit, you know, my wife and her ability to interact with us on a

daily basis.

We were lucky enough to come across a company out west that dealt with stem cells and it has been the only thing that has helped mitigate some of the conditions with my wife's MS. Now, one of our major issues -- we're from the south. We live in Arkansas, humidity, they affect her on a daily basis. The brain fog that they get with when they can't really just seem to be with it during the day, just the energy levels. We went out to Stemgenex and when we approached them and discussed my wife's issues, we were made acutely aware that -- we know that there's no cure for what she has and I understand that but if I can mitigate some of the symptoms that she has, she is much more productive, she is more engaged on a daily basis with us and the family and you know, when we talk to them, they told us: "Hey, let's go ahead and try it. "

When we went there and engaged in the stem cell treatments with my wife's own stem cells, the response was immediate. When we got

home, flew back to Arkansas, my wife, who was confined to a wheelchair was able to get up and walk down our hallway. That's a big deal for us and for the kids, you know.

My wife is the head of a -- we sponsor the Little Rock Lacrosse Club --

DR. WITTEN: Excuse me a second. Could whoever is having that dinging, can you turn it off? So we can listen to the speaker?

MR. MARR: It's okay. I can talk over it; I'm loud. So my wife is the director of our Little Rock Lacrosse so we are playing Lacrosse in the heat and we are playing Lacrosse in the humidity. That's all we have down south so anyway, as soon as we took these stem cell therapy -- it was amazing, the turn around that happened with her. The ability to stand up and cook, the ability to get out of bed, the ability to go to the bathroom, to not have somebody walk her to the bathroom and help her go to the bathroom has -- it just frees up -- we have a new normal because of MS and that's what we have to live with and we

understand that but to mitigate some of these symptoms that are out there, this is the only thing that works for us and so when it works for her, it also works for me, it works for our kids, it works for my family, my parents, her parents because it just doesn't affect one individual; it affects multiple individuals so I know there is a lot of stuff going on with regards to what you're looking at but I don't think we need to stop what's working for a patient utilizing their own stem cells.

Let them continue on. We can look at this later down the line. This works for us and I want to thank you all for the ability to come and talk to you today from more of a caregiver's point of view and if you have any questions, I'll be happy to answer them but I would like to pass on to my wife.

(Applause)

DR. WITTEN: Thank you. The next speaker is Kristin Marr.

MS. MARR: Hi, good afternoon. I'm

Kristen Marr. I am a 51 year old mom and a wife. When I was diagnosed in 2007 with primary progressive multiple sclerosis, our kids were three and five years old. My disease, because it is in the 5 percent of multiple scleroris, normal 95 percent have primary relaxing remitting -- you have a chance for the body to go into exacerbations, for the body to heal itself. With primary progressive, we are the five percent that progressed very rapidly at a downhill slide and there are no medications currently on the market for primary progressive to slow the progression of this disease.

The only answers my doctor had for me when we were diagnosed, and I say we because as Brian said, it affects a family. It doesn't just affect me as an individual. First thing he asked was if we had any long term care insurance. To prepare for the worst, to enjoy my time with my kids now, that in three years, pretty much I would be confined to a wheelchair and to make those arrangements.

The only thing he could do for me palliatively, because of the extreme amount of pain I was in, the difficulty I had walking, the brain fog, the sleep deprivation just simply because you could not hold your head up at 2:00 in the afternoon if you tried.

It didn't matter how many Redbulls, soda or whatever you had, forget it, it wasn't happening. The fatigue was debilitating.

I would tell my friends it's about like if you were unlucky enough to get the flu, your worst day of the flu, how you felt, that's how I felt every day.

I was to the point where I couldn't take care of our kids. It's horrifying. As a mother, it is absolutely a nightmare. The doctors basically tried any type of anti- inflammatory, massive quantities of steroids, other approaches that didn't help so in 2010, I detoxed off of everything and I said I can't live like this.

I was a fighter, I worked for numerous charities, I ran my own business and I couldn't do

those things anymore and I wasn't about to give up so we detoxed, we looked at nutrition, I read every study there was on MS treatments and stem cells. I was willing to go out of the country, my husband wasn't. He didn't trust the medical care, he trusted the medical care here. Thank goodness we found a stem cell company on the west coast that was able to take on our case.

They, exactly like Brian said, they never said there would be a cure, our only hope, that it would alleviate symptoms and I was fine with that. We came back within 24 hours. I walked off the plane, I walked into my kids on my feet. I walked down the hall. Within three weeks, I was fixing their dinner, I was helping with homework. I could do all those things.

Within three months, I was back to driving them to school every day and picking them up at school. We were about to have what was a normal family life. Now granted, I wasn't running around like a lot of people would be. I was going at my own pace and that was fine. I'm fine to go

with my own pace now. The only reason I am going to transport chair today is simply because I had a kidney stone, I am out of the hospital ten days, I needed to have surgery and my doctor advised if you're going to make this trip, you better make it as easy as possible and you don't need to throw your MS back into a flare and the kidney stone was because of an FDA approved medication, it was to help with my speed of walking and we found that that was actually what caused my kidney stone and caused ten days in the hospital.

It may work for some people. It doesn't work for me. My stem cells worked for me. I've had two stem cell treatments in 2010 and 2013. I want to read from you my MRI report. This is three months after I had stem cells and some people can say it's placebo effect.

When you're on your feet and you're cooking dinner and you haven't done that in a year, it's not a placebo effect. This is not a placebo effect. To my neurologist, this was proof that something was going on in my body that was a

good thing. Not that it always healed but that it was a good thing.

To read through the basics, distribution areas of demonetization is grossly stable as compared to the two prior studies. There are no definitive new active or enhanced MS plaques. The plaques or the demyelinization in my brain, my spinal cord, my C2, C3 and T6, T7, I have no active lesions, all the activity in my brain as far as demyelinization is gone. As you can see where it says it's grossly stable.

I'll take that any day. I'll take being on my feet being in front of you. I am happy to be where I am at. If you give me the capability and the power to use my own stem cells to regenerate and help my body heal. The body has a natural ability to heal itself.

DR. WITTEN: I'm afraid I am going to have to ask you to wrap it up.

MS. MARR: Thank you, I appreciate.

(Applause)

DR. WITTEN: Our next speaker is Carl

Nicastro.

MR. NICASTRO: Hello, my name is Carl Nicastro. I'd like to start off by thanking the Food and Drug Administration for giving me this opportunity to speak about the draft guidance's relations to regulation of adult stem cell treatment. I was diagnosed with relapsing multiple -- back in 1997. Despite taking the drugs that were recommended from my neurologist, my condition spiraled downhill.

Some of my symptoms to start with were numbness in the feet, shaky hands, loss of vision periodically, pressure headaches, dizziness and loss of balance. To fast forward to 2013, my symptoms increased. The numbness fled from my feet through my legs, causing me to be in this chair.

The shakiness went from my hands to my head. I couldn't sit in a chair like I am sitting now. I would fall out. I couldn't bathe myself, I couldn't dress myself and couldn't feed myself.

Now, I got down to 120 pounds, searching

the web, we found stemgenex, they offered stem cell therapy treatment, whatever you wish to call it. I had it done. The very next day on the airplane, on the ride home, I could feel my feet, my helper Brittany Waller here helped me get my shoes on so I would be more comfortable and in doing so, I felt sensation on my feet. They tickled. I wondered what further results I'd see. Upon arriving at home, I saw many and many other improvements so I was able to feed myself and bathe myself.

I am not saying I can run a marathon, but I am able to stand up. I am not doing it today because it's been a long couple of days, very emotional, very hard on me and it affects me -- stress is a big issue with MS as well as heat. Now with everything that the stem cells have done for me over the time, they plateau, they level so I did it again and I am seeing further and further improvement.

After these improvements, I decided to do it once more and I continued to see more

improvement so I did it a third time and it was back in February of this year and I am still seeing improvements. Just last week, I was able to tie my shoe and I wasn't able to do it in many of years, probably five or six years and to me, it's quite an accomplishment.

Now, drastic concerns that you have without -- the rest, side effects I already told you the price of the results. As far as the risk goes, it's not very clear that some of the drugs that you had already approved for me to take and they caused disease which ultimately leads to death and I tried it. I tried it for a year. I am not going to mention what drug it was. I am sure you already know so the stem cells being that the only risk that there is for the stem cells, it's not to stem cells, it's a procedure that I am giving them.

Stemgenex is very clean. They seem to be very knowledgeable, to have the top staff for the job. So far as the side effects go, I have not seen anything negative. I managed to gain 30

pounds since then. My hair is growing back and I can speak.

I didn't mention it before but my speech was so slurred that you couldn't even understand me at all. With all that being said, the stem cells are a universal drug for many illnesses and I speak on the behalf of anybody that has an illness that is having trouble getting treatment for it. I believe that we are in the beginning stages of the stem cell to be used on a regular basis to be in competition with the medical field of other countries as well as ourselves. I don't think we should be hindered. If I cut my finger and sew it back on, it's still my finger, it's not my drug.

(Applause)

DR. WITTEN: We really appreciate your --

MR. NICASTRO: And I owe this all to my friend who looked this up in the internet and brought me to stemgenex. His name is Sean Bailey and with that, thank you again for letting me

speak.

DR. WITTEN: Thank you.

(Applause)

DR. WITTEN: Our next speaker -- our next speaker is Michael Sabolinski.

DR. SABOLINSKI: Thank you for the opportunity to speak at this meeting. My name is Mike Sabolinski. I am commenting as a private physician trained in dermatology and cardiology with 36 years of experience in academic medicine and industry. I fully support the existing FDA HCT/P guidance documents and the agency's interactive approach with all stakeholders.

Today I advocate for two positions: one, limiting inappropriate claims for 361 products and two, suitable FDA oversight of all HCTPs. In short, if claims of safety are to be made, then FDA should approve them. Addressing my first position on product claims, given that companies are permitted to self proclaim that their products are 361 HCT/ps, abuses of the system do occur. A so called 361 HCT/P often carries claims that it

interacts with the body therapeutically and in complex ways. Some examples include delivery of growth factors, reduction of inflammation, enhanced healing of soft tissue, reduction in scar formation, stimulation of misankable stem cells, decreasing pain and modulating the immune system. These are biologic claims.

Unsubstantiated claims of positive clinical outcomes have become common. In wound healing alone, effectiveness claims of increasing the frequency and decreasing the time to healing are often disseminated in testimonials, on websites and in private, printed promotional materials.

The code of federal regulations did not anticipate the claims of slowing, preventing, or curing disease would be promulgated without premarketing approval. The imperative of FDA review and approval of the design of clinical trials, primary end points, statistical methods and all safety and efficacy data is indisputable.

I was here in the early 2000s at the

evidentiary hearings in wound care and at those hearings, we established the existing wound treatment guidance and regulations that largely are in place today.

And today I see that more products -- that there are products that were required then to undergo rigorous clinical development and regulatory review, premarket review. 361 products have no such requirements and yet I see similar claims. What I ask for today is a level playing field. What I think we've heard today have been requests for changes to existing guidance and regulations.

I don't think that these requests have any sound basis or regulatory justification. So inappropriately circumventing the FDA approval process by self proclaiming 361 status should be curtailed. The homologous use guidance states the 361 HCT/Ps must be intended for homologous use only and only homologous use is permitted to be reflected by the labeling, advertising or other indications of the manufacturer's objective of

intent. If these criteria are not met, then the HCTP is not homologous by definition and cannot be considered a 361 product so claims of safety and effectiveness are generally considered by practitioners as being FDA approved.

For 361 products, they are not. I strongly support the position that the labeling of 361 products clearly and prominently state that the product is not FDA approved and no clinical trials have been done under an IND.

Addressing my second position on appropriate FDA oversight, regarding homologous use, I urge FDA to clarify 21 CFR, 1271. 3 and sections of their guidance specifically pertaining to the terms of repair and reconstruction. I recommend that the guidance define repair and reconstruction solely in terms of mechanical and physical functions. This is consistent with the agency's original position adopted in 1997 and its proposed approach to the regulation of cellular and tissue based products. I thank the agency for the opportunity to comment.

(Applause)

DR. WITTEN: Thank you. Our next speaker is Sheila Sabon DeCastro.

MS. DECASTRO: Greetings and thank you for the opportunity to provide comments. My name is Sheila Sabon DeCastro and I am a nurse practitioner at Mass General Hospital and a consulting clinical director to the tissue program at Beth Israel Deaconess Hospital Plymouth.

I have over 15 years of experience in clinical and regulatory and tissue donation, in regenerative medicine and wound care. These personal reflections on the proposed draft guidance do not reflect the opinions of the aforementioned institutions.

The guidance documents under discussion today are urgently needed and a major step forward in providing clarity for the manufacturers of HCT/Ps and healthcare providers for the benefit of patients.

Although the regulatory scheme set forth in part 1271 works well for a traditional

allograft products such as cadaver skin used to cover burns, the tiered, risk based approach laid out in part 1271 is not functioning as it was intended.

The market is saturated with products that are represented as section 361 HCT/Ps but may not actually meet the criteria of section 1271. 10 but actual status of these products is not ambiguous under existing policy and precedent.

These guidances simply compile prior FDA policy interpretations as discussed in preamble language proposed and final rules, tissue reference group decisions and various enforcement letters issued over the past several years. Nevertheless, the guidances are needed because certain segments of the allograft industry have disregarded applicable precedents or have leveraged vague language from these sources to provide a rationale for marketing certain products without FDA premarket oversight.

This regulatory gap creates a potential safety problem in that it may permit the

distribution of cell therapy products without appropriate FDA oversight. Because some of these products have not been demonstrated with valid scientific evidence reviewed by FDA on a premarket basis to be clinically safe and effective, healthcare providers are becoming surrogate safety and efficacy reviewers.

Providers are put in a position of determining the safety and efficacy of the products based on the information available and maybe led unknowingly to make clinical decisions to the detriment of patients.

Patients may receive treatments that do not do what they claim or may not receive FDA approved products that have been shown to be safe and effective. The remainder of my comments concern the homologous use draft guidance.

First, I want to emphasize that the distinction between structural and non-structural tissues is not novel. In the preamble to the section 1271. 10 regulations, FDA expressly affirmed the continuing validity of the concept

for the application of the term "homologous use. " The distinction makes clinical sense because it is useful in distinguishing HCTPs for which clinical data are necessary from those where safety and efficacy are readily apparent.

Second, the guidance is not arbitrary or capricious by virtue of providing for the disparate treatment of similar products. In particular, the argument that ground amniotic tissue must be treated the same as ground bone is premised on a false equivalency because while they are both structural tissues, micronized amniotic tissue, unlike ground bone, is not intended for a structural purpose.

For this reason, there are meaningful differences between the products and disparate treatment is appropriate as noted in the guidance document. Third, it is appropriate and consistent with historical precedent for the guidance to take the position as it does.

The homologous use requires a tissue to be intended for the same basic function in both

the donor and the recipient. In particular, the guidance appropriately asserts that tissues that are structural in the donor must be intended to perform structural function in the recipient.

When FDA finalizes this guidance, it should clarify that reducing inflammation or scarring are not homologous uses of tissues when it did not perform this function in the donor. Finally, I urge FDA, when it finalizes the guidance, to expand the discussion of its existing regulation which provides that intended use may be determined by referring not only to advertising and labeling but also to other indications of the manufacturer's objective intent.

It has been long standing agency policy that a product's intended use can be inferred, even in the absence of expressed claims when the product's actual uses are well known and understood by the products and users.

FDA should reiterate this principle in the draft guidance to make clear that the agency has the legal authority to take action, to enforce

premarket review requirements for HCT/Ps that have been pervasively promoted for non-homologous uses even when the written labeling and the advertising has subsequently been cleaned up. I thank you for your attention to these comments.

(Applause)

DR. WITTEN: Thank you. I'd like to find out if any of the other speakers that were going to speak at this session have shown up. Brian Gates? Scott Graham or Kristen King? Are any of them in the audience?

Okay, well we are scheduled for a break from 3:21 to 3:41. We're a bit early so how about if we reconvene at 3:00? Is that good? We'll reconvene at 3:00.

(Recess)

DR. WITTEN: Okay, we are going to get started again. Our first speaker is John Samies.

DR. SAMIES: Good afternoon, my name is John Samies and I am a board certified infectious disease specialist and a certified wound specialist practicing at the regional medical

center in Orangeburg, South Carolina. I received my medical degree from Hahnemann Medical College in Philadelphia and I have been in practice for about 30 years.

My focus on the draft guidance documents relates primarily to those HCTPs that are intended for wound healing. It is estimated that at any given time, about one percent of the population is suffering from a chronic wound and these wounds obviously have profound costs both emotionally, financially, socially on our society.

It is therefore very important that we products that are approved for care of those wounds. Unfortunately, we had emergence of products with somewhat unsubstantiated claims entering the market. In fact, I would say I am bombarded by marketing of new products that imply homologous use and then they imply things beyond that homologous use in their marketing yet they assert that they are under homologous use statutes, including section 361.

Additionally, the adverse event

reporting in section 361 of these products is limited to reporting of transmission of infectious diseases largely and it does not go beyond that into other potential adverse outcomes.

Section 361 HCT/Ps are obviously an important part of the tool kit of wound care specialists and as an example, cadaver dermis and amniotic tissues are well suited as wound coverings and the regulations under part 1271 provide pretty sufficient oversight into these products.

The objective of the regulations is to largely prevent transmission of infectious disease from the donor to the recipient but when claims of complex biologic interactions are made for these HCT/Ps such as modifying wound healing, those regulations in part 1271 are not sufficient alone since they really don't assure the safety and efficacy of the products beyond the transmission of infectious disease. For example, how does one assess the oncogenic potential of these products?

I am here to today to urge FDA to

finalize the guidance that mandates that biologically driven products intended for active wound healing are adequately regulated. I'd like to stress three points: first, it's appropriate for FDA to use the terms minimum manipulation and homologous use narrowly. If not narrowly used, 361 will continue to be a loophole through which products will continue to be inappropriately marketed to clinicians.

The guidelines state that an HCT/P that's intended for use as an unproven treatment for a "myriad of diseases or conditions" is "likely not intended for homologous use only. " I would agree and I would urge FDA to delete the likely and the reference to myriad conditions since it leaves some doubt.

To void any doubt, it's important that the final guidance states clearly that if an HCT/P is intended for use as an unproven therapeutic treatment for any disease or condition is probably not intended for homologous use therefore it's not supposed to be regulated under part 1271.

The types of data that are needed to support wound healing claims have been set forth in documents by the FDA including guidance for industry on chronic, cutaneous, ulcer, and burn wounds developing products for treatment. When FDA finalizes homologous use guidance, the agency should make clear that the claims of therapeutic treatment require clinical trials under established FDA guidelines and regulation. Such products will generally not be considered to be homologous use products then under section 361.

Second, I would urge FDA to clarify that homologous use does not imply the function of the tissue in any way that it could conceivable function but rather it's appropriate to limit the definition of homologous use to the same basic function that it serves in the donor.

In particular, it's appropriate to hold that homologous use of tissue that is structural in the donor is limited to the same basic structural function in the recipient.

Lastly, I would submit that this is a

dynamic process. I would submit that initial assertions of homologous use and intermobile manipulation products should be defined by clear and basic science. The current regulation scheme allows for incentives for immediate product availability without FDA premarket review but not proof that the products continue to serve with that anticipated homologous use.

The lack of oversight allows the payers and others to claim marketing beyond the original scope of homologous use, thank you.

(Applause)

DR. WITTEN: The next speaker is George Sauter.

MR. SAUTER: Hello, my name is Gus Sauter. Prior to retiring from Vanguard at the end of 2012, I was the company's first chief investment officer. I am happy and appreciate the opportunity to present to you today.

I am here representing myself. I am a strong advocate of stem cell treatment and I would like to tell you about the experiences and

benefits that I have had with stem cell therapy that was qualified under the same surgical procedure exception. I'd also like to describe the experiences of two family members and a friend of a friend have had and I will admit right off that my infirmity was minor compared to many of the people who have spoken here today.

I had osteoarthritis in my hip, which caused me constant pain from about 2009 to about 2013, preventing me from really doing anything strenuous whatsoever and then in the middle of 2013, I had a stem cell procedure using stem cells harvested from my bone marrow and after about four months, I had no pain except for perhaps an occasional minor twinge.

After 12 months, I really had no pain. My procedure enabled me to play golf again without any pain whatsoever but to be fair, I still couldn't take the pounding of strenuous activity like running so I did have a second procedure and this time using stem cells from my adipose tissue and again, while I had improvement, I still can't

take the pounding of running but I am really quite pleased with the progress that I've made and the increased quality of life that I have regained.

I also appreciate the fact that I have avoided having to do a hip replacement. I mentioned that I have other family members that have benefited from stem cell procedures.

My wife is a competitive ballroom dancer and she developed osteoarthritis in her knee and subsequently tore the meniscus in her knee. She had injections that really did not -- were not effective in reducing the pain whatsoever and ultimately, her orthopedic surgeon concluded that trying to repair the meniscus was rather fruitless because she had bone on bone on her knee and he recommended that the only remedy was a knee replacement.

Instead, before pursuing that more extreme option, she elected to try a stem cell procedure. Her recovery has been absolutely remarkable. After six months, she was back dancing and she competed in two competitions seven

or eight months after the procedure. At the time, she had perhaps a twinge in her knee every now and then.

Today, 14 months later -- yesterday she told me she has no pain and she said she never even thinks about it. Another family member, my mother in law, suffers from Alzheimer's. She was really quite depressed about her loss of memory and expressed that she really didn't feel like herself. In total despair, she claimed that she couldn't live that way. In my research on stem cells for myself, I had read that they were used to treat Alzheimer's as well so we arranged to have a procedure for her and her progress was really remarkable and quite swift.

She expressed, immediately feeling much better about herself and at ease with herself. All the family members agree that she made remarkable progress for about 10 months but even potentially reversing some of the Alzheimer's that she previously had but Alzheimer's as you know is a terrible disease and due to its relentlessly

destructive nature, she has started to decline again.

Finally, I told a friend of a friend about the improvement that my mother in law had experienced from her stem cell treatment. The friend's mother was also suffering from Alzheimer's and despite some initial skepticism, they enrolled the mother in the stem cell program and by all accounts, they are extremely happy with the improvements the mother made. In some of the other cases, obviously not a cure but improvement in their quality of life, giving them some remaining quality of life so I'd say that we're four for four and we're very pleased with the outcomes from the use of stem cells qualified under the same surgical procedure exception and while I still can't take the pounding of running, I am really excited about the prospect of improvement in stem cell technology.

As I mentioned to begin with, I come from the investment industry so I certainly recognize and support the need for appropriate

regulation. I also recognize that in the investment industry that there is also harmful overregulation that we have so I hope the FDA will exercise its oversight to support the development of stem cell technology that has really benefitted so many people in such a profound way. Thank you for your time today.

(Applause)

DR. WITTEN: Thank you. The next speaker is Rosemary Tambouret.

DR. TAMBOURET: Hello, thank you for holding this meeting. My name is Rosemary Tambouret, I am a pathologist at Massachusetts General Hospital and a good portion of my work deals with obstetrical pathology so that's -- and my comments today actually reflect my own opinions and not that of the hospital and I wanted to come speak to you today because I believe that you know, the FDA may not be completely aware of all the functions of the amniotic membrane so that's really what I am going to speak about.

So the amniotic membrane, as you know,

is a complex tissue and it has multiple functions, both structural and non- structural so you can think of the amniotic membrane as just simply being a barrier, as avascular tissue barrier but in fact it also has other activities, metabolic activities and it can secrete different growth factors, cytokines and what not and these, as I will discuss in a bit, also impact the donor use of amniotic -- or the recipient use of the amniotic membrane and I've included a very detailed reference here on this first page review article that goes through all the different aspects of use of the amniotic membrane so the mechanism of action of the amniotic membrane deals with of course first a physical barrier in utero but even there it's a metabolically active as it helps regulate the volume of amniotic fluid, allows transport of water and oxygen and it also controls the PH of the amniotic fluid.

The amniotic membrane also contains several growth factors, antiangiogenic factors, anti-inflammatory factors, natural inhibitors to

proteases as well as natural inhibitors to scarring so in utero, they speak often of healing without scarring in the infant.

The amniotic -- part of the amniotic membrane is basement membrane and this basement membrane also facilitates the establishment and the integration of epithelial cells and thirdly there is the extra cellular matrix which provides the tensile strength for the amniotic membrane plus actually acting as a reservoir for different proteins like collagen and growth factors.

So these same functions apply to the clinical applications of the amniotic membrane. The clinical use actually of amniotic membrane dates to over 100 years ago so it's been in use quite a long time and the examples currently of its use include treatment of burns, ulcers, acute and chronic wounds and ocular applications so results from clinical use have shown that there is reduced fibrosis, reduced scarring, reduction in inflammation, enhanced healing, even pain alievement and promotion of epithelial growth.

So -- and the clinical results, I believe, stem from the same factors that are active in utero that the amniotic membrane has a barrier properties. It's permeable. It produces growth factors, these antiangiogenic, anti-inflammatory proteins, these natural inhibitors to proteases, and it's the amniotic membrane promotes establishment of an epithelial cell layer and again, the extra cell provides the tensile strength of the whole membrane. Those are my comments and I hope you take into account all the many functions of the amniotic membrane.

(Applause)

DR. WITTEN: Thank you. I just want to know whether Tracy Thompson or Amy Tucker have signed in? Tracy Thompson, Amy Tucker? Okay, our next speaker is Leigh Turner.

MR. TURNER: Hi, I am Leigh Turner. I am an associate professor at the University of Minnesota Center for Bioethics. Brevity has made me blunt so I'll try to be concise. I'd like to put the draft guidances in context by drawing

attention to the hundreds of U.S.clinics selling unimproved stem cell inventions. I am concerned years of inadequate regulatory oversight by the FDA fuel the nationwide spread of such businesses.

Over 350 U.S. businesses advertise purported stem cell treatments provided at nearly 600 clinics. Many of these clinics sell costly stem cell interventions for ALS, Alzheimer's disease, Parkinson's disease, MS, muscular dystrophy, cerebral palsy. Autism, I think you get the idea, and dozens of other conditions.

Children are among the individuals receiving unapproved stem cell products. Advertised interventions include autologous stem cells attained from adipose tissue, bone marrow and blood, allogeneic products derived from amniotic material like placentas, xenogenic stem cells and even embryonic stem cells.

It's understandable that individuals with serious health problems respond to the compelling marketing claims that stem cell clinics make. Less comprehensible is how companies get

away with making unsubstantiated claims about cellular therapies without prompting swift regulatory action. Clinics advertise using the rhetoric of stem cell treatments and IRB approved patient funded studies, numerous companies use the NIH's clinicaltrials. gov registry as a marketing platform for so called studies that have serious scientific, ethical, and regulatory flaws.

Some falsely claim their studies are NIH or FDA approved. When journalists have contacted the FDA and asked questions about such studies, the FDA has responded by stating that it cannot comment on trials conducted under investigational applications.

Since these studies are not conducted under IND, such replies provide regulatory cover for clinics selling unapproved stem cell products.

For many years now, the FDA has failed to regulate the U.S. direct to consumers stem cell marketplace on a risk based, timely and consistent manner. This is a marketplace where regulatory action is rare, even when businesses have spent

the last five years selling unapproved stem cell products for 20 to 30 diseases.

Acknowledging this failure, I commend the FDA for issues the draft's guidances. The documents clarify when premarketing authorization is required, they provide insight into how the FDA defines, interprets and applies concepts such as the same surgical procedure exception, homologous use and minimal manipulation.

Addressing these concepts is crucial because such criteria are abused by clinics. Perhaps the guidances are assigned, the FDA now plans to take action against marketing claims and business practices that often are based on nothing more than the unsubstantiated assurances of clinic owners, however I am concerned meaningful regulatory action will not follow this hearing.

In 2012 and 2013, I contacted the FDA and urged them to investigate numerous businesses selling autologous adipose derived stem cell interventions for ALS, Alzheimer's disease, Parkinson's disease, MS, muscular dystrophy, COPD,

stroke, spinal cord injuries and dozens of other diseases and injuries. Over three years later, these companies continue to profit for administering stem cell products. The FDA states require premarketing authorization. During their advocacy for the 21st Century Cures Act, Senator Lamar Alexander and former Senate majority leader Bill Frist have used a pay to participate study run by a Florida based physician as an example of dramatic progress being made in stem cell therapies.

They presumably did not know that at least two patients whose eyes were injected with autologous bone marrow derived stem cells suffered serious complications. These outcomes were reported not by the doctor charging 20,000 dollars per so called research subject to inject stem cells but by the physicians who treated the patients he injured.

I urged you to investigate this business back in January 2013 before these patients were injured. Disciplinary actions by medical boards

in California, Florida and elsewhere had published case reports reveal that numerous patients have been harmed by clinics selling unapproved stem cell interventions. Recall for example, Domenica Fitzgerald and Richard Pohling, two patients who died after their autologous stem cell transplants -- lawsuits filed by former patients of various stem cell clinics also contain troubling allegations of injuries and fraud.

Widespread clinical use of unapproved stem cell products combined with continued regulatory inaction will likely be followed by additional reports of harmed patients. This is to be expected when so called stem cell treatments have not been subjected to preclinical studies and tested for safety and efficacy and properly designed and conducted in regulated clinical trials.

The out of control marketplace for stem cell interventions needs effective regulatory oversight. I therefore hope the draft guidances are more than stage props and this hearing is more

than public theatre. When patient safety and public health are stake, the FDA must do more than function as a paper tiger. It is time for action, thank you.

(Applause)

DR. WITTEN: Thank you. Our next speaker is Eliza Tyler.

MS. TYLER: Good afternoon. You've hear a lot, I'm sure. I'd like to thank the panel for the opportunity to speak today and I come asking you -- my name is Eliza Tyler and I have cohabitated with Type I diabetes since I was nine years old. It's an autoimmune disease for which I lived 44 of

years with. I come to you today to voice my concerns and hopes

regarding safety and regulation of adult stem cells as a method of treatment for many diseases and conditions for which pharmaceutical means have run their course and do more harm. These adult cells which reside in my very own body have the ability to heal and improve my quality of

life with little to no side effects.

Type I diabetes is an autoimmune disease. Nothing I did at the age of nine could have caused it or prevented it. Type I in depth is something I can't explain in five minutes. The list of complications and rising death rates associated with Type I are long and I am currently dealing with several complications.

I am a firm believer in the science and medicine which includes stem cells and I would encourage the FDA to allow my medical providers to offer such treatments to treat, maintain and enhance one's quality of life. My providers have seen marked improvement in my disease status and have not deterred me from undergoing treatment again.

Stem cells have been used for decades in the United States and around the world with success. Having learned from clinical trial rejection that I would be difficult to match with a donor and no doubt run a higher risk for rejection for the islet cell transplant, my

options were limited.

I began a focus driven search on stem cell options. My prognosis looking dim and continued deterioration, pain and suffering. I chose to undergo adipose derived adult stem cell treatment with Stengenex out of California. My first treatment in 2010 was conducted outside the United States and I knew this was not a cure. I was never promised a cure, however, I was willing to take the risk having followed research for many years, my issues included hyperglycemic unawareness, a dangerous inability to sense an oncoming low blood sugar which can lead to coma and death, pain associated with peripheral neuropathy and arthritis, retinopathy and falling vision, gastroparesis a paralysis of the gut, which includes malabsorbption issues and glucose levels which are near impossible.

I also suffer with psoriatic arthritis and have suffered a traumatic brain injury. All of these issues for which I was concerned showed almost immediate improvements. My first low blood

sugar in over 20 years was felt coming on within 24 hours of my first treatment.

Others continued to improve over the months afterwards. My response to these treatments was neither placebo effect nor anecdotal. My lab work done with ongoing medical lab work results were on the thing here. With medical supervision has shown stability and improvement with my A1C and overall glucose levels.

We have the knowledge, the passionate scientist and doctors on many levels looking at many disease processes, let us allow them to move forward in the research and application of adult stem cells. Please let us not classify my cells, that reside in my body, as a drug for they've brought me complete quality of life that I would not have otherwise.

I've been listening as a patient for 40 years about the babble of a cure on the horizon for Type I. In all reality, we are being held back from something that could already be making

our lives easier with no side effects, cost effective and no chance of rejection.

If we continue to withhold adult stem cells from the U.S. citizens who can benefit from them, then more medical tourism to places of unknown or poorly overseen practices will be our only option.

I understand and respect the FDA's job of balancing a patient's safety with alternative treatments. Please accelerate the availability and I see the lady off to my left, I thank you again for the opportunity to speak before you today.

(Applause)

DR. WITTEN: Thank you. Our next speaker is Newton Vaughn.

MR. VAUGHN: Thank you for this opportunity to speak in front of this committee. My name is Newton Vaughn and I reside in Lakewood, Colorado. I am asking the FDA to represent myself and others in the approval of stem cell research in surgery. Approval by the FDA may make this

treatment more affordable to others.

I was able to pay for this out of my own pocket and it's a possibility that it would be paid by insurance, if this is approved. Approximately 20 years ago I asked my doctor about the shaking in my right hand. He said he didn't want to alarm me but it could be the beginnings of Parkinson's disease. Five to six years ago, I noticed this shaking getting worse and I was referred to a neurologist who prescribed medications.

A friend of my sister had stem cell treatment with some improvement for Parkinson's I researched the stem cell surgery and Stemgenex was recommended by this friend. I decided to go ahead with the procedure.

On June 5th, 2015, I received stem cell surgery for Parkinson's disease. This treatment was provided by Sam Jennings of La Jolla, California. After this surgery, it was recommended that I spend an hour and a half to two hours daily for 45 days in a hyperbaric chamber.

I purchased my own chamber and in August of 2015, I took delivery and I have been using it since. It was also recommended that I continue to take the medication and vitamins that I was previously prescribed. Since that time, I noticed some improvement in my ability to control the shakes in my right hand.

Since January -- in January of 1916 -- or 2016, I was able to thread a needle and sew on some buttons, something I could not do before that treatment. I also had been able to reach above my head and put tools on board hooks in my shop. There are times that I am able to control the shakes. In August of 2016, I was able to trim tall hedges and paint windowframes on my house.

For almost a year, I have been able to make lamps out of wood and I have pictures with the lamps. Since March, I have been taking dance lessons. August this year, I was able to prepare and freeze peaches. I made a peach pie and I've been playing golf. I live alone and without the treatment, I am not sure that would be possible.

I'm here, there are so many incurable diseases for which treatment options are very limited. Often treated with drugs, with known and unknown serious side effects but the treatment, which means using my own stem cells, there is little or no risk of rejection.

American citizens should not have to go out of the country to receive stem cell treatment. Too often, in this country we operate under a thing called F. E. A. R., false evidence appearing real. Where would I be without treatment? Probably would not be here today to speak to you and I would not have the ability to live alone.

In closing, I am asking the FDA to accelerate the availability of safe and effective stem cell treatment to Americans in need and I am asking the FDA to allow my chosen medical professional to have the ability to offer stem cell treatment to myself and others. Again, I thank you for this opportunity to speak.

(Applause)

DR. WITTEN: Thank you. I think the

next presentation is a videotape presentation from Samantha Wilkinson. I am not sure, is someone playing it? They are going to do something.

(Video plays)

MS. WILKINSON: Hello, my name is Sammy Jo Wilkinson. I am going to talk to you about patient perspective. Today I will tell you about my positive personal experience with stem cell therapy for multiple sclerosis and what the patient community wants in cellular medicine, to highlight the plight of both the acute and the chronic patients; it could be helped by cellular therapy.

We should not have to pursue this as medical tourists. My experience, I've had MS since 1995 when I was 30 years old and just starting a dotcom business in the financial publishing area.

This disease has no known cause, no cure, and the approved disease modifying drugs only offer to slow the disease's progression but with a heavy side effect profile. I tried these

approved drugs, they all failed me. I am in a wheelchair, suffering from over 28 symptoms and I am looking at nursing homes because I am becoming so paralyzed. I have always followed cell research because I kept hearing from MS patients who found relief in foreign clinics.

Then I heard about Celltex Therapeutics in Houston, Texas. They use one's own adipose stem cells. When the dose is needed, only perinatal stem cells are expended in the lab through therapeutic dose. Similar to a higher dosing, I was seeing the university clinical trials.

I spent three weeks in Houston receiving a weekly IV of 200 million of my own mesenchymal stem cells. My response was very positive, very immediately. Feeling returned to my hands. I could feel my fingerprints again. My heat tolerance was regained, my energy levels soared, the stiffness abated so my husband and I were able to enjoy touring for the first time in many years with my schedule of treatment for October 2012.

Then, disaster struck. The FDA blocked access to using one's own stem cells in September 2012. This delayed my therapy plan but Celltex found a topnotch certified hospital in Cancun, Mexico under regulations established by both the FDA and COFEPRIS, the Mexican equivalent, they were able to import and export cells.

I was able to resume treatment but the extra cost associated in a 14 hour day of international travel was an extra burden patients should not have to bear and all of this for a one hour IV that I should be able to get in my local doctor's office without the tireless support of my husband of

years. I would not have been able to access this therapy. Now after my fourth treatment in May of 2014, I can only describe my state as long term remission from secondary progressive MS. I don't know how long this will last for but I am very happy with it and my health is improving and so is my function. I can sit out outside everyday in 80 degree sunshine and the

heat doesn't bother me. I don't feel sick and miserable anymore.

I have enough energy to exercise every day. The time for change is now. Proposals already exist from leaders in this field on how to accelerate the approval process. Professor Kaplan who first discovered mesenchymal stem cells in 1991 and is a distinguished presenter at this conference, has published a detailed roadmap entitled Progressive Approval. Japan has already implemented such mechanisms in their Regenerative Medicine Act of 2014.

It's time for the U.S. to move forward with cellular therapies. Faster access to cellular therapy, especially for no option patients needs to be a national priority. The regulators need to work with us, not against us. Patients, caregivers, doctors, researchers, regulators, we all have a role to play in making this happen. Thank you so much.

(Applause)

DR. WITTEN: Our next speaker is Joan

Woodward.

MS. WOODWARD: Good afternoon, to introduce myself, my name is Joan Woodward. I am 59 years old and I have primary progressive multiple sclerosis. To date, there are no cures, no medicines which prolong the inevitable progression of disability which is characteristic of this form of MS. My definitive journey began on May 6th, 2014 after limping for over a dozen years and being treated for possible hip replacement, I researched and found a new orthopedic surgeon that referred me to Emory Neurology in Atlanta.

I had a single lesion which appeared on my brain stem MRI. It took until September 2nd, 2014 for a second lesion to appear. I am in excellent health, have never had a so called attack, still, the dreaded words: "You have primary progressive multiple sclerosis. "

Since then, I have spent at least an hour a day researching this disease not for one minute accepting the dreadful diagnosis of no

relief in sight. I have joined a clinical trial for a new drug and have exhausted nearly all avenues.

Multiple MRIs have shown my disease to be progressing. The clinical trial drug is a double blind so I deduced that either I was receiving the placebo or the drug was not helping my symptoms, therefore, earlier this year, my family and I elected for me to receive mesenchymal stem cells harvested from my own adipose tissue. Literally my fat may save me.

After carefully researching several clinics, protocols and doctors, I chose a facility. My cells, my blood, my decision and my father's money. How could this possible be considered a new investigational drug? Every individual I spoke to that received this therapy was well informed and had completed the same amount of research.

At no point have I been promised results or a cure. Already I have stopped taking an extremely expensive drug for fatigue. That in

itself is a huge plus. Prior to stem cell treatment, I was becoming increasingly fatigue to the point of not being able to fathom exercise let alone work for a full day in the comfort of my own home.

Occasionally I suffered through difficult bouts of vertigo which my doctor attributed to MS. Currently, I self administer interferon injections in an effort to strengthen my blood brain barrier. I have been taking interferon since October of 2014. Despite the interferon in the clinical trial drug, I can tell the disease was progressing.

Now seven months after treatment with my own stem cells, I am walking a mile a day with walking sticks for balance, my restless leg syndrome has been minimized and I feel the best that I've felt in years.

I know I am not cured but I am hopeful that this improvement in my general health will prolong the disease progression until a cure is discovered and enough to repeat my stem cell

procedure, should my disability progress. Curiously, 25 years ago, I was diagnosed with a condition which resulted in multiple miscarriages, actually four in a row.

I had a condition called pregnancy immune syndrome. My body did not recognize my husband's cells and therefore rejected my pregnancy as foreign bodies. I qualified for a clinical trial of a process called lymphocyte immune therapy. Today, I have a 25 year old daughter and a 23 year old son thanks to the efforts of science and the medical community.

January 30th, 2002, the FDA closed the clinics offering LIT. They said the use of blood cells qualified as an investigational new drug. As a result, this procedure is no longer offered in the United States and young women must leave our country in order to receive this simple injection of your husband's blood cells.

The Food and Drug Administration recently issued draft guidelines clarifying that the stem cells used in most clinics are drugs and

require rigorous approval process before they can be used in patients.

I sincerely hope and pray that this does not result in others not having the opportunities that I've had. The FDA has its hands full with regulating new investigational drugs. Their efforts are greatly appreciated by the general public. Let's keep their efforts where they belong, studying drugs, not the cells that god gave us.

(Applause)

DR. WITTEN: Yes, is Jennifer Ziegler here? Great, and the two speakers who were scheduled to speak earlier in this section? Tracy Thompson, Amy Tucker? Okay, well we are going to move on to the panel questions for the speakers. Hopefully the speakers are still around so maybe I'll start.

I have a question both for Rosemary Tambouret and also Rebecca Baergen.

So first, Dr. Tambouret, you both discussed functions of amniotic membrane and I am

just wondering if you have any comments specifically about interpretation of homologous use for amniotic membrane for clinical use?

You discussed the functions of amniotic membrane in your presentation.

DR. TAMBOURET: Right.

DR. WITTEN: And I am wondering if you -- you know given all the various ways that it's used clinically, if she can comment on your interpretation of homologous use for amniotic membrane?

DR. TAMBOURET: Well granted that the amniotic membrane is found in the uterus surrounding the baby, right, that's natural function but one aspect you could say that may be homologous to use on skin, on the recipient's skin is analogous to the baby because it's been known, as I mentioned before that you can have injury to the infant in utero and they seem to heal without any scar and it's believed that that function in part comes from the amnion.

Now in other body sites, I don't know if

I can comment on it but it seems to, as far as I know, from the studies that I've read, in the sites where amnion is used currently, it may not be totally homologous but it is -- it does act as a barrier and so in that sense it is homologous but you know, used in ocular situations or use in different would healing situations where you have actually an open wound and if you use amnion and -- to my knowledge there has been a great deal of success, does that answer your question?

DR. WITTEN: Yes, thanks. I have the same question for Dr. Baergen.

DR. TAMBOURET: I don't think she is here now.

DR. WITTEN: Okay, thank you. Other questions? Go ahead.

DR. LARD: So we heard from several physicians and healthcare prcacitioners regarding concerns about wound healing claims related to allografts and specifically, claims regarding complex tissue interactions and I was wondering if those individuals, and I think it was Dr. James,

Dr. Sabolinski, Sheila Sabon DeCastro, Marie Gehling and I believe Dr. Samies also spoke to this.

If you could, or if any of you are still here, speak to the adequacy of the homologous use guidance in terms of making it clearer what is homologous use in this arena? If any of them are still here. Thank you.

DR. SAMIES: Well I think part of that goes back to the question of conceivably. If something conceivably has a use that's homologous, that's different than what we are stating is the homologous use.

So if we say it's a structural function, then it should be a structural function that gets through the 361 pathway.

I kind of see this more as a dynamic thing. If a company wishes to make claims of other activity of their 361 pathway product, then there should be no reason why they can't go back and then with randomized controlled trials, go through biologic licensing to come to those

claims.

The real issue is to decide what is the true function that we are describing as the homologous use and maybe that needs to be clearly defined when a product is brought forward to market.

DR. LARD: Okay, so do you have suggestions for the guidance that could make it clearer?

DR. SAMIES: Well part of it is I think they need to make a statement as to this is the homologous use that we are anticipating this product for. I don't think that means that they can't go back and find other things that they believe are important about their product but that should go through an entirely different pathway.

DR. LARD: Okay, thank you.

DR. WITTEN: Could you state the name. I should ask this for all the speakers. Just state your name for the transcriptionist.

DR. SAMIES: John Samies.

DR. WITTEN: Thank you.

DR. SABOLINSKI: Mike Sabolinski. I am going to focus on something that I don't think was talked about but I tried to was to me, something that excludes a part from being considered homologous is -- are the claims so if you make claims, then by definition that exceed your structure and what is intended in the other criteria for homologous, you are not homologous.

So some of these claims for instance, relate this to amniotic membrane.

A claim of covering, wound care covering, that I believe is a homologous use and homologous claim. When you get into deliver of growth factors and the litany of other things that amniotic membrane does, you haven't proven it. There were statements like "I believe that" or "decrease in scarring." These are things that have been well defined in the regulations and I agree with the existing regulations. I think the regulations have adequately anticipated the issues that come up so with regard to homologous use, I would ask that manufacturers and people who are

distributing, people who are acting as agents of the company are mindful of the claims that they make, whether it's in their presentation to doctors, their patient brochures and even the literature that is being generated and dropped on doctor's offices because the assumption is that these are FDA reviewed and approved data.

They are not. They may look virtually identical but doctors can be mislead so that's what I have to say.

DR. LARD: Thank you.

DR. WITTEN: Okay, well I think if there are no more questions from the panel, we are going to close and on behalf of the FDA panel, I'd like to thank the speakers for their presentations.

Everyone in the audience, whether in person or by webcast for your attention to this meeting, we've had a two very full days of interesting and insightful comments that will be considered by FDA along with the comments of the docket as we finalize the guidance. The hearing is now concluded. I'd like to thank everyone.

So I am reminded that September 27th is the day the docket closes so if you have additional written comments, please submit them by September 27th. Thank you for your participation.

(Whereupon, the PROCEEDINGS were adjourned.)

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CERTIFICATE OF NOTARY PUBLIC

DISTRICT OF COLUMBIA

I, Carleton J. Anderson, III, notary public in and for the District of Columbia, do hereby certify that the forgoing PROCEEDING was duly recorded and thereafter reduced to print under my direction; that the witnesses were sworn to tell the truth under penalty of perjury; that said transcript is a true record of the testimony given by witnesses; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this proceeding was called; and, furthermore, that I am not a relative or employee of any attorney or counsel employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

(Signature and Seal on File)

Notary Public, in and for the District of Columbia

My Commission Expires: March 31, 2017