

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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1 Even so, the processing swabs showed staph and
2 strep. After cleaning and disinfection, there was
3 no infection left. Again, dosed and then
4 re-implanted. Six weeks later and there was no
5 issues.

6 So since we follow good tissue practices
7 as a tissue bank, we would ask that the exception
8 also apply to an establishment that ships the
9 autologous HCT/P to an FDA- registered tissue
10 establishment in accordance with the tissue
11 establishment instructions. Thank you.

12 DR. WITTEN: Thank you. The next
13 speaker is -- that was the speaker for LifeLink
14 and LifeNet combined, is that the case? So our
15 next speaker represents MedCentrus. Is that
16 correct?

17 DR. MOORE: From LifeNet Health, I'm
18 sorry.

19 DR. WITTEN: Oh, there's a separate
20 LifeNet Health presentation? Okay.

21 DR. MOORE: Yes, they were lumped in
22 together. So I'll be speaking today supporting

1 the concept and current definitions of minimal
2 manipulation of HCT/Ps. And my name is Mark
3 Moore. I'm senior director of scientific affairs
4 at LifeNet Health and past chair of the Scientific
5 and Technical Affairs Committee at AATB.

6 So as we'll be hearing about many times
7 over the next few days, there are many different
8 clinical applications of allografts, only some of
9 which are shown here. And while allografts are
10 widely used, they may not be clinically usable
11 exactly as recovered from a suitably screened
12 donor. Thus tissues may be processed often via
13 methods requiring no more than minimal
14 manipulation in ways to make them usable.

15 So these minimally manipulation
16 processing methods are thus employed to increase
17 the clinical utility of the allografts through,
18 for example, reduction of risk and disease
19 transmission, reduction of immunogenic response,
20 shaping grafts into usable forms, reducing
21 barriers to optimal physiological activity, and
22 storing tissue for longer useful life and ease of

1 handling. In the slide at the top, you see a
2 flowchart related to homologous use and minimal
3 manipulation, which is an AATB draft guidance
4 document and the title of that you can see at the
5 top.

6 However, what I want to do here is focus
7 on the definition at the bottom, which we've
8 already seen here in the presentations with 1271.3
9 including two definitions of minimal manipulation
10 of: one, for structural tissue, the minimal
11 manipulation indicates it does not alter the
12 original relevant characteristics of the tissue
13 related to the tissue's utility for the intended
14 use in the recipient with regards to the
15 reconstruction, repair, or replacement. And that
16 for cells in nonstructural tissue, this also means
17 that the processing does not alter the relevant
18 biological characteristics, again, for the
19 intended use in the recipient.

20 So how do manufacturers achieve this?
21 So typical minimal manipulation methods currently
22 include antimicrobial disinfection, for example,

1 with antibiotics; detergents could be physical or
2 chemical means; terminal sterilization, often with
3 some form of radiation; physical alterations,
4 including dissection, trimming, machining, and
5 grinding; and all minimal manipulation methods.
6 Could be de- mineralization to expose growth
7 factors; could be de- cellularization to reduce
8 immunogenic potential of materials; and storage
9 preservation methods, including freezing,
10 freeze-drying, dehydration, water replacement
11 agents -- all recognized as minimal manipulation
12 methods.

13 So, all these methods are designed,
14 again, to improve the clinical safety and utility
15 of the allografts while retaining their original
16 relevant characteristics of that material as
17 intended for use in the recipient. So, some of
18 those retained original relevant characteristics
19 would include biomechanical properties, such as
20 tensile strength, compressive strengths, and
21 isotropic strength as seen here.

22 Also, I would maintain that those

1 structural properties needed for intended repair
2 and regeneration could be microstructural, not
3 necessarily those macrostructural tensile
4 strength, but microstructural properties such as
5 providing an osteoconductive matrix or an
6 appropriate scaffold for wound healing and
7 physiological properties that could be retained,
8 even in spite of a minimal manipulation; could be
9 retention, or increased availability of growth
10 factors, for example, with DBMs; or matrix
11 signaling to provide a good wound healing
12 environment, for example, with a de-cellularized
13 matrix.

14 So in summary, the minimal manipulation
15 methods described here, including physical,
16 biochemical, and chemical treatments are designed
17 to enhance the clinical safety and utility of
18 allografts, while also ensuring that the
19 allografts maintain their original relevant
20 characteristics to support the basic function of
21 those allografts. Thank you very much.

22 DR. WITTEN: Thank you. The next

1 speaker represents MiMedx Group.

2 MR. PETIT: Good morning. I'm Pete
3 Petit and I'm chairman and CEO of MiMedx. I would
4 like to begin by thanking Dr. Califf, Dr. Witten,
5 and FDA staff for conducting the scientific
6 meeting last week, and broadening the Part 15
7 Hearing to the two days with a larger venue that
8 we have here today.

9 By way of background, I'm a medical
10 entrepreneur who started my first company 45 years
11 ago. That company grew to become several
12 different publicly traded companies in health care
13 technology and health care services. I've worked
14 with the FDA under numerous commissioners and
15 administrations and I've seen significant changes
16 in the agency's interactions with industry and
17 through these administrative changes. Therefore,
18 I believe I'm in a good position to provide an
19 industry perspective.

20 I believe that most, and I'll emphasize
21 most, health care business executives take a
22 logical approach to decisions related to product

1 innovation. That being the case, they want rules
2 and regulations that are clearly delineated,
3 easily interpreted, and uniformly enforced. I
4 understand that FDA might prefer rules and
5 regulations that are somewhat nebulous, so that
6 they have more latitude and interpret the rules as
7 industry innovation perhaps pushes beyond their
8 original regulatory concepts. However, the agency
9 needs to recognize a disruption that causes within
10 industry. And industry recognizes a need for
11 regulatory changes from time to time, there's a
12 well-documented legal process for implementing
13 changes to regulations.

14 I've had an opportunity to meet -- then
15 Commissioner-elect Califf in Atlanta last December
16 when he and Dr. Witten spoke at the International
17 Stem Cell Conference. Commissioner Califf's
18 message was quite clear and refreshing. My
19 summary of his numerous comments is simply that if
20 industry brings us science-based proposals, we
21 will make judgments associated with those that are
22 also science-based. From MiMedx and industry

1 standpoint, I want to believe that under Dr.
2 Califf's leadership, there will be a refocus on
3 scientific approaches to decision-making at the
4 FDA. While I don't want to take away from the
5 positive outlook that I currently have, I still
6 have significant concerns about the draft guidance
7 documents that are the subject of this Part 15
8 meeting.

9 By the way of background, MiMedx is the
10 leading processor for amniotic tissue and since
11 2006 has shipped over 700,000 allografts. The
12 clinical efficacy and cost- effectiveness of our
13 products are supported by 32 publications,
14 including clinical and scientific studies,
15 randomized controlled trials, and MiMedx products
16 have an impeccable safety record.

17 More than a year before publishing the
18 draft minimal manipulation guidance documents for
19 comment, FDA issued a main function test -- used
20 the main function test, which is one of the new
21 principles introduced in the new draft guidance as
22 a basis for issuing an untitled letter from MiMedx

1 asserting that our micronized or powdered products
2 were not minimally manipulated and, therefore, did
3 not qualify for regulation under the Section 361.
4 Prior to that untitled letter, MiMedx had
5 undergone three FDA inspections, including a
6 directed inspection that reviewed this status of
7 our micronized products with input from CBER with
8 no adverse findings.

9 FDA did not discuss the issuance of the
10 untitled letter with MiMedx prior to its issuance
11 and offered no explanation for its position. The
12 letter itself, it took another two and a half
13 months to obtain an explanation from the agency.
14 At this time, there are at least 10 -- at this
15 point in time, there were at least 10 micronized
16 human skin dermis and bone products that were in
17 the market.

18 The receipt of the untitled letter in
19 August 2013 started a three-year process of trying
20 to reconcile the FDA's position in the untitled
21 letter with the regulations and the FDA's
22 previously published interpretations. The draft

1 guidance on minimal manipulation and homologous
2 use also reported major changes in tissue
3 regulation that the federal law states can only be
4 implemented through the formal process of notice
5 and comment rulemaking where Congress and OMB are
6 involved.

7 Therefore, we recommended FDA formally
8 withdraw the guidance documents on minimal
9 manipulation and homologous use, and initiate the
10 Federal rulemaking process to give industry a
11 reasonable time to comply with any new rules and
12 exercise enforcement discretion on continued
13 products for companies that enter into a diligent
14 pursuit of the BLA process. And finally,
15 substantially any new rule changes.

16 Let me stop there, Chairman, and just
17 recommend that this fly that's --

18 PANEL: I know.

19 MR. PETIT: -- around the podium be
20 eliminated before the next speaker comes.

21 (Laughter)

22 DR. WITTEN: Thank you.

1 MR. PETIT: Somewhat distracting.

2 (Laughter)

3 DR. WITTEN: Our next speaker -- thank
4 you. Our next speaker represents the
5 Musculoskeletal Transplant Foundation.

6 DR. KIM: Thank you. Actually, wait for
7 my slides to come up.

8 DR. WITTEN: Perfect.

9 DR. KIM: Great. Thank you. My name is
10 Dr. John Kim. I'm a breast reconstruction
11 specialist speaking on behalf of the
12 Musculoskeletal Transplant Foundation. I'd like
13 to thank the FDA for allowing me to present the
14 clinician's perspective on homologous use of
15 acellular dermal matrix in breast reconstruction.
16 These are my relevant disclosures.

17 The surgical treatment of breast cancer
18 often requires the removal of the breast or a
19 mastectomy. While this can be a lifesaving
20 procedure, survivorship can be difficult because
21 of this qualitative disfigurement that results, as
22 you can see here. So, modern breast cancer

1 treatment mandates breast reconstruction. There
2 are almost a quarter of a million new cases of
3 breast cancer diagnosed every year. Of these, 30
4 to 40 percent will require mastectomy and there's
5 been an increasing use of implant reconstruction,
6 partly driven by the heightened awareness of the
7 genetic basis of breast cancer.

8 So the particular advantage of acellular
9 dermal matrix in this setting is that for nipple
10 sparing mastectomies, as well as for BCRA-positive
11 patients, direct to implant cases, and anatomic
12 cases in which the pectoralis muscle has been
13 attenuated, this harbors particular hope for a
14 natural reconstruction. A traditional subpectoral
15 implant base reconstruction requires us to place
16 the implant underneath the pectoralis muscle seen
17 here. However, the problem from a reconstructive
18 point of view is you've got some tightness in the
19 lower pull, and then oftentimes the inner portion
20 of the breast is offset from the outer portion of
21 the skin. So you end up with a very unnatural,
22 high-riding breast.

1 The value proposition and the benefit of
2 cutting the pectoralis muscle and using ADM in
3 this fashion is that we can then use the acellular
4 dermal matrix as a homologous extension of the
5 tissue so that it can support and reinforce the
6 lower portion of the breast, and allow the patient
7 to get a much more natural reconstruction.

8 So here's a video showing the mastectomy
9 flap, and I'm going to turn it on the underside,
10 and what you can see there in the pink and white
11 is the actual acellular dermal matrix. And it's
12 been reconstituted so it looks like normal tissue
13 because, in fact, it has become like normal
14 tissue.

15 If we look at it histologically on the
16 right side, we can see native soft tissue, and
17 bordered on the left side is the acellular dermal
18 matrix and on close ultrastructure, you can see
19 that it looks and acts just like normal dermis.
20 So our results in terms of achieving a natural
21 reconstruction after a very disfiguring mastectomy
22 have been enhanced by our ability to use acellular

1 dermal matrix and our patients are getting results
2 that we could never get before from a mastectomy.

3 So the context for this is that there
4 are over 100,000 breast reconstructions done in
5 the U.S. every year. Of those, 80 percent require
6 prosthesis and of those, another 80 percent are
7 using acellular dermal matrix currently. There
8 have been over 300 peer-reviewed publications
9 validating breast and acellular dermal matrix
10 reconstruction since 2005.

11 So in summary, per the FDA definition of
12 dermis as a elastic connective tissue layer of the
13 skin that provides a supportive layer of the
14 integument, I think using this definition of the
15 dermis, the use of ADM for breast reconstruction
16 surgery would be considered homologous use because
17 the purpose of acellular dermal matrix in this
18 circumstance is to provide a supportive layer to
19 the skin envelope. Thank you.

20 DR. WITTEN: Our next speaker represents
21 Organogenesis.

22 DR. BILBO: My name is Patrick Bilbo. I

1 am senior vice president of Organogenesis where I
2 oversee the company's regulatory affairs and
3 government relations. Founded in 1985,
4 Organogenesis has been a pioneer in the
5 development of cell-based products for chronic
6 wound healing. The company's commercialized three
7 Section 351 allogenic, cell-based products --
8 Apilgraf, Dermograft, and GINTUIT -- that have
9 been approved through the Class 3 medical device
10 and biologics pre-market approval pathways, and
11 have been used to treat hundreds of thousands of
12 patients.

13 Organogenesis commends FDA for issuing
14 these important draft guidances and in particular
15 for the clarifications concerning allografts that
16 are intended to interact with the body at a
17 cellular level to promote wound healing. We have
18 been concerned for some time that the market is
19 being flooded with allograft-derived products
20 making a wide range of unproven claims about their
21 therapeutic efficacy and promoted for applications
22 beyond what we believe to be for homologous use.

1 The importance of this issue cannot be overstated.
2 Leg and foot ulcers that fail to heal are an
3 immense public health challenge, typically
4 affecting the elderly and people with diabetes.
5 And if not effectively treated, these ulcers can
6 lead to osteomyelitis, amputation, and death.

7 The availability of safe and effective
8 treatments is, therefore, a critical public health
9 concern. We believe that patients must receive
10 therapeutic treatments that have met FDA's
11 rigorous preapproval evidentiary standards. Many
12 healthcare providers, however, are unaware of
13 these regulatory differences in standards.
14 Without guidance that provides clarity for
15 industry, confusion over which products have met
16 the strict standards will persist.

17 The difference between the regulatory
18 schemes applicable to biological products on the
19 one hand and Section 361 allografts on the other,
20 it's stark. The regulatory requirements for
21 biological products intended to treat chronic
22 wounds are establishing clear guidance that

1 includes rigorous recommendations for pre-clinical
2 development, clinical trial design, and labeling
3 claims. Wound healing claims, for example, must
4 be supported by valid scientific evidence
5 establishing an improved incidence of wound
6 closure or a reduction in time to healing.

7 In contrast to this rigorous pre-market
8 review period for biologics, distributors of 361
9 HCT/Ps marketed for wound healing need only comply
10 with the requirements for facility registration,
11 donor screening, and good tissue practices. There
12 are no clinical data requirements at all.

13 However, this situation's not limited
14 only to wound care. Allograft distributors are
15 also marketing injectable sheet and other forms of
16 allograft-derived products through the Section 361
17 pathway for a variety of therapeutic purposes in
18 other areas, such as orthopedics and general
19 surgery. The minimalist regulatory scheme
20 embodied in the Part 1271 is entirely appropriate
21 for allografts that, in fact, meet the criteria
22 set forth in Section 1271.10.

1 It is clear that Congress never intended
2 that Section 361 would be used by commercial
3 entities to circumvent the FDA regulatory review
4 process to market manufactured allografts as
5 medical therapies to treat, prevent, or mitigate a
6 disease. But there are companies within the
7 allograft industry who are systematically
8 exploiting the jurisdictional criteria in Section
9 1271.10 to circumvent the conventional FDA
10 pre-market review requirements applicable to other
11 biological products.

12 Many companies are self-designating
13 their products to Section 361 HCT/Ps even though
14 the products do not, in fact, meet the criteria
15 set forth in 1271.10. These companies have
16 introduced to the market a host of human tissues
17 claiming to interact with the body in complex
18 ways. These products are processed in ways that
19 are not minimal, are promoted for uses that fall
20 far outside the realm of homologous use, and claim
21 comparative or superior efficacy to FDA approved
22 biologics and devices. This situation puts some

1 of our most vulnerable patients at risk and must
2 not continue.

3 There are some who argue that these
4 guidance documents incorporate new concepts or
5 make new law and thus must, as a matter of law, be
6 subjected to notice and comment rulemaking. In
7 fact, however, these guidance documents simply
8 synthesize and apply in examples the agency's
9 longstanding positions as articulated in
10 rulemaking preambles, untitled letters, and
11 warning letters issued over the years, as well as
12 decisions of the tissue reference group. The
13 attempt to impose notice and comment rulemaking is
14 a stalling tactic designed to delay enforcement
15 action against products that should never have
16 been on the market without pre-market review in
17 the first place because they have more than
18 minimally manipulated or being promoted for
19 non-homologous uses.

20 In general, the drafts for minimal
21 manipulation and homologous use are comprehensive
22 and provide very useful guidance. Both guidances

1 would benefit from additional examples for both
2 hard and soft tissue technologies to inform
3 industry when developing products.

4 The draft guidances are a welcome step
5 towards imposing order on an industry that has
6 been operating more or less free from meaningful
7 oversight. It is critical for the public health,
8 as well as for the future of the regenerative
9 medicine industry, that FDA finalize the draft
10 guidances with all possible speed. Thank you for
11 your time and attention to these comments.

12 DR. WITTEN: Thank you. Our next
13 speaker represents RTI Surgical.

14 DR. DEURLING: Good morning. I'd like
15 to thank FDA for holding this public hearing and
16 for the opportunity to speak this morning. My
17 name is Justin Deurling and I'm here on behalf of
18 RTI Surgical. RTI manufactures and distributes
19 HCT/Ps for use in life-enhancing orthopedic,
20 spine, sports medicine, and surgical specialties
21 procedures. As an institutional member of the
22 American Association of Tissue Banks, we at RTI

1 echo the comments made by our colleagues at
2 today's hearing and urge FDA to fully consider
3 these prior to moving forward with finalizing any
4 of these draft guidances. The continued
5 availability and access to future lifesaving and
6 life-enhancing treatments depends on the careful
7 consideration of the potential impact of the
8 agency's actions.

9 While RTI has numerous concerns with the
10 draft guidances, I've elected to use my brief time
11 at today's hearing to discuss the important role
12 of sterilization and decellularization processes
13 for ensuring the safety of HCT/Ps. And how the
14 somewhat ambiguous nonspecific language of the
15 draft guidance could block access to and inhibit
16 the development of the safety enhancing processes,
17 while vitally important donor screening and
18 testing alone cannot guarantee the safety of
19 HCT/Ps. Decellularization and sterilization
20 processes enhance the safety of HCT/Ps by
21 virtually eliminating the risk of donor to
22 recipient disease transmission and implant

1 rejection, and are effectively deployed while
2 retaining the relevant original characteristics of
3 the process tissues.

4 Yet, by not specifically identifying
5 these processes as not more than minimal
6 manipulation in the draft guidance, the agency
7 leaves the continued access to allografts
8 utilizing these important processes up to
9 interpretation. To illustrate this point, I'll
10 briefly discuss one of RTI's tissue sterilization
11 processes, but it is important that you keep in
12 mind that similar sterilization and
13 decellularization processes have been implemented
14 by the various tissue banks across the country,
15 improving the safety profile for the allografts
16 they distribute.

17 The nonspecific language presently in
18 the draft guidance could potentially jeopardize
19 patient access to these safe implants. RTI's
20 developed three tissue specific sterilization and
21 decellularization processes as seen here. Today,
22 I'll briefly focus specifically on the BioCleanse

1 process to illustrate these points.

2 The BioCleanse tissue sterilization
3 process consists of gently oscillating pressure in
4 the presence of chemical agents which gently
5 profuse and completely penetrate the tissue. The
6 combination of chemical agents removes blood and
7 lipids and inactivates or removes pathogenic
8 microorganisms. The BioCleanse process is
9 validated through pathogenic organisms, including
10 HIV, hepatitis B and C, bacteria, fungi, and
11 spores. Repeated water rinses throughout the
12 process remove debris and final water rinses
13 remove residual chemicals, leaving the tissue
14 biocompatible and retaining its relevant original
15 characteristics. So that's what BioCleanse does.

16 Now, what doesn't it do? At a
17 microstructural level, you can see the appearance
18 of the tissue as unaltered compared to unprocessed
19 tissue. The biomechanical and biochemical
20 properties of BioCleanse processed tissue are also
21 similar to unprocessed controls. Upon
22 implantation, the biological response to

1 BioCleanse processed tissue is similar to
2 autograft. So the tissue safety is markedly
3 improved through the use of the BioCleanse process
4 without impacting the tissue's utility for
5 reconstruction, repair, or replacement.

6 In fact, through the use of
7 sterilization and decellularization processes such
8 as BioCleanse, today RTI's distributed more than 5
9 million sterilized biologic implants with zero
10 incidents of implant-associated infection. And
11 yet as written, the draft guidance does not
12 acknowledge the important role of processes such
13 as BioCleanse in ensuring patient's safety and
14 eliminating the spread of communicable diseases by
15 specifically designating sterilization and
16 decellularization processes as not more than
17 minimal manipulation.

18 Again, while important, donor screening
19 and testing alone cannot guarantee the safety of
20 HCT/Ps. In sterilization and decellularization
21 processes, enhanced tissue safety by eliminating
22 the risk of donor to recipient disease

1 transmission and implant rejection. Yet, the
2 draft guidance as written does not recognize the
3 importance and utility of these processes for
4 preventing the spread of communicable diseases.

5 Therefore, RTI in alignment with AATB
6 recommends FDA restate the list of processes that
7 are considered minimal manipulation that was
8 presented in the preamble to the original tissue
9 rules and expanded to include both
10 decellularization and sterilization using any
11 validated technique, as seen here on this slide.
12 Only through the use of clear, unambiguous
13 language such as this can the agency ensure the
14 continued availability of these safety enhancing
15 processes. Thank you for your attention.

16 DR. WITTEN: Thank you. Our next
17 speaker represents StemGenex.

18 DR. BRODY: My name is Steven Brody.
19 I'm an M.D., Ph.D., and I'm the chief scientific
20 officer at StemGenex. You know, my academic and
21 scientific career began at Cambridge then
22 continued at Yale and then it led to three years

1 of clinical research right here at the NIH. So
2 for me this is a homecoming. While I was at
3 Stanford, I co- authored a textbook with Robert
4 Edwards, who received the Nobel Prize in Medicine
5 in 2010.

6 As a reproductive endocrinologist, I
7 have seen how the evolution of regulations have
8 helped guide advances in in vitro fertilization.
9 And in this context, my work in stem cell
10 therapeutics is a natural transition. Thanks for
11 the opportunity to comment on these four draft
12 guidances. It is really a matter of public
13 health, public safety and also public access to
14 these stem cell therapies.

15 Now, adipose tissue contains cell types
16 with nonstructural functions. We mustn't think of
17 fat tissue as just adipocytes. It's monocytes,
18 parasites, granulocytes, and, most important, the
19 stem and progeny cells which have the capability
20 of repair and regeneration. This is so important.

21 Now, let's focus on the stem and
22 progenitor cells for a second. They have

1 immunomodulatory functions. They have cell
2 signaling functions. They have hormonal functions
3 and, again, they have the property to potentially
4 repair and regenerate tissue, not just treat
5 disease, but repair and regenerate tissue. On
6 this basis, the fact that these cells have these
7 properties, it is reasonable and it is warranted
8 to view adipose tissue as both structural and
9 nonstructural.

10 And finally, in accord with these
11 comments, we must recognize that there are
12 biological effects of fat on target organs and
13 tissues. The most important thing is that fat
14 isn't even meant to be structural in the human
15 body. It's a repository of energy in times of
16 caloric scarcity. It's not even meant to be a
17 structural organ per se, although it plays a role
18 in our society as a structural organ. But look at
19 all the effects that it has on other tissues in
20 the body. In fact, fat tissue's the endocrine and
21 an immune gland, therefore, it really must be
22 viewed as not just structural, but also

1 nonstructural.

2 Now, the question of minimum
3 manipulation is an important issue. Now, if we
4 use a GMP enzyme for recombinant DNA, no
5 contamination, perfectly safe, and we take cells
6 with specific biological characteristics. We use
7 this enzyme to isolate the cells from the parent
8 tissue which is harvested, there are no
9 significant biological characteristics that are
10 changed in these cells. And then in our model of
11 giving them back autologously in a very safe
12 manner.

13 Now, if we could expand the definition
14 of minimal manipulation, this would help our
15 patients have access to stem cell therapies. This
16 is so important. Now, this timeline comparable to
17 one of the other speakers that shows really the
18 progression of the use of cellular therapies in
19 medicine. And in fact, these lifesaving
20 procedures are now considered standard of care,
21 dating from blood transfusions, bone marrow
22 transplants and other organ transplantation

1 systems.

2 Now, we have the advent of stem cells
3 and stem cells have captivated the imagination of
4 the scientific and academic communities. One of
5 the reasons why I switched fields, it's a
6 burgeoning field and there's no question it will
7 impact every single aspect of medical practice.

8 Now, with this excitement comes
9 responsibility, and with responsibility comes
10 regulation. The American Association of Blood
11 Banking, as listed here, has been successfully
12 setting standards in cellular therapies for over
13 20 years. Accreditation by the AABB is based on
14 the core principles of efficacy, scientific
15 validity, and patient safety. The standards of
16 the AABB, which were developed in the past, have
17 been recognized both nationally and
18 internationally. Furthermore, the AABB and the
19 FDA collaborate on an ongoing basis.

20 DR. WITTEN: Excuse me. I'm afraid --

21 DR. BRODY: I believe this is the idea

22 --

1 DR. WITTEN: -- you're going to have to
2 wrap this up.

3 DR. BRODY: Thank you very much.

4 DR. WITTEN: Our next speaker represents
5 U.S. Stem Cell Inc.

6 DR. COMELLA: Thank you. I'm Kristin
7 Comella. I'm the chief science officer of U.S.
8 Stem Cell. We are a publicly traded company, so I
9 must remind you of the forward-looking statements.
10 We have a comprehensive mix of products. We've
11 been a company since 1999, and our focus has
12 always been to bring stem cell therapies to
13 patients.

14 I think this quote is particularly
15 important today. All truth passes through three
16 stages. First, it's ridiculed. Second, it's
17 violently opposed. And third, is it accepted as
18 being self-evident?

19 The re-implantation of autologous HCT/Ps
20 is recognized in the regulations and during the
21 same surgical procedure, this is considered the
22 practice of medicine. And there are a variety of

1 different things that are recognized under this,
2 including fat grafts, skin graft, bone marrow
3 transplants, platelet rich plasma, tendon and
4 ligament grafts, vascular grafts, hair grafts, and
5 bone grafts. All of these procedures are
6 considered surgical and they did not go through
7 double-blind, placebo-controlled trials.

8 I want to focus on the comparison
9 between bone marrow and fat tissue, and, in
10 particular, something called stromal vascular
11 fraction that a lot of people have been discussing
12 today. The reason that bone marrow is accepted
13 under a 510K is because there was preexisting
14 technology to the 1976 amendments covering medical
15 devices. Fat tissue does not have that same
16 luxury because there was no preexisting
17 technology. But why would fat and bone marrow be
18 viewed separately? When you're taking cells from
19 bone marrow, why is this different than taking
20 cells from fat? And in particular, fat is a less
21 invasive method of collecting and also isolating
22 the cells with lower risks associated with it.

1 In addition, there are higher numbers of
2 cells and stem cells and lower numbers of white
3 blood cells which are inflammation creating in the
4 fat tissue versus the bone marrow. So
5 scientifically speaking, it makes zero sense that
6 we'd regulate these two tissues in a different
7 manner. Why would the FDA regulate our own body
8 tissue and consider this a drug?

9 Who is responsible for paying for these
10 trials if the FDA doesn't do it? Pharmaceutical
11 companies typically cover the expenses associated
12 with doing a double-blind, placebo-controlled
13 trial. Because there is no drug to sell at the
14 end of this because it's cells from your own body,
15 no pharmaceutical company is going to cover these
16 trials, so who is going to cover these trials if
17 they're going to be mandated by the FDA?

18 In addition, why would the FDA regulate
19 cells from bone marrow and fat tissue different?
20 These are some images from our clinic where we
21 treat patients. These are our medical
22 practitioners who care very much about their

1 patients, and their safety and outcomes, and who
2 have become, in some sense, disgusted with the
3 medical system and some of the products that are
4 currently available that are not making patients
5 better. We need new options for patients.

6 The process is very simple. It can be
7 done in under 60 minutes. A small sample of fat
8 tissue is taken in a minimally manipulated process
9 where the patient remains awake. There is no
10 general anesthesia. The cells are obtained and
11 can be administered back to that same patient.

12 We've trained over 600 practitioners
13 throughout the world and in the U.S. who are doing
14 these procedures safely. We have over 6,000 cases
15 documented and when you consider some of our
16 colleagues, there are tens of thousands of cases
17 documented. If this was really a safety concern,
18 there would be more than a handful of adverse
19 events which are being reported. And that's all
20 we have right now, just a handful out of ten
21 thousands of patients. And there is no drug on
22 the planet that has that kind of record.

1 Regenerative medicine is here to stay
2 and it's continuously growing. We, as a field,
3 have an obligation to bring these therapies
4 forward. Patients have a right to make an
5 informed consent decision about how they're going
6 to use these treatments on themselves. They have
7 a right to alternative therapies. We need more
8 funding for these patient trials and the
9 government should not regulate all bodies. I'm
10 Kristin Comella and I will always stand up for
11 patient rights. Thank you. (Applause)

12 DR. WITTEN: Thank you. There were
13 three speakers who were not here at the time.
14 Have they shown up? No.

15 Okay, in that case, I will call for
16 questions -- or open into questions from the panel
17 to the speakers. Any questions?

18 DR. ANATOL: I do.

19 DR. WITTEN: Okay.

20 DR. ANATOL: Okay, I have a question for
21 the first speaker from Alliqua Biomedical. On
22 your summary slide, you have a bullet that says

1 consideration of multitasking of human tissues and
2 cells in both donors and recipients. Can you
3 clarify what you mean by "multitasking?"

4 DR. SMIELL: I'm talking about in
5 multitasking of human tissue; I'm talking about
6 the matrix signaling that can happen from
7 components of the structural tissue. Is that an
8 --

9 DR. ANATOL: Thank you.

10 DR. SMIELL: Mm-hmm.

11 DR. WITTEN: Also, have a question for
12 you from Alliqua Biomedical, maybe you could --

13 DR. SMIELL: I'm sorry. (Laughter)

14 DR. WITTEN: Sorry, I didn't catch you
15 before. Thank you for your thoughtful slide
16 presentation. I do have a number of questions,
17 some of which are regulatory in nature, so they
18 really are questions for us.

19 DR. SMIELL: Yes.

20 DR. WITTEN: But I'm just wondering if
21 you, yourself, have the answers to some of these.
22 For example, just an example, safety of added

1 processing or preservation agents. You're asking
2 who determines it. So I'm not really asking you
3 that, but I'm just wondering --

4 DR. SMIELL: Well, I --

5 DR. WITTEN: -- if you have any ideas
6 along the lines, either for that question or as it
7 relates to any of the other questions you asked in
8 your slides?

9 DR. SMIELL: So bottom line, I do
10 believe we need a process similar to the request
11 for designation that does a review of all the
12 processing steps, source of tissue and claims that
13 wish to be made that would be mandated for
14 everyone to go through prior to marketing tissue
15 products.

16 DR. WITTEN: I see, so that's more
17 broadly than just the answer to this question.
18 Yeah, okay. Thank you.

19 DR. SMIELL: Yeah, I'm sorry.

20 DR. WITTEN: Okay, I have a question for
21 the speaker from Johnson & Johnson which is, I'm
22 just wondering, you made a number of comments

1 about what you thought should be subject to
2 oversight or shouldn't be subject to oversight.
3 And I'm wondering if you could map those two
4 comments on the guidance documents themselves?

5 DR. SIEGEL: I'm sorry. Comments about
6 what should or shouldn't be?

7 DR. WITTEN: You made some comments in
8 your talk. I'm sorry I wasn't able to write the
9 whole thing, but we'll get it on the transcript.
10 But you made some comments about what you thought
11 should be regulated differently than tissues, so
12 like the operating -- the institute should be --

13 DR. SIEGEL: Oh, okay. Right, right,
14 right.

15 DR. WITTEN: And so I'm wondering, like,
16 if you would map two comments on the guidance
17 document, what would you be saying exactly?

18 DR. SIEGEL: Well, yes. Specifically, I
19 would say that while the guidance document creates
20 a different standard for the same surgical
21 procedure exception from the standard for minimal
22 manipulation, and that's highlighted in footnote 4

1 and elsewhere in the guidance document under
2 question 4 and in the last paragraph of the major
3 section, that there isn't a good rationale for
4 that difference. So, the exception is only
5 eligible for products that are rinsed, cut, or
6 cleaned. And I would suggest that other forms of
7 minimal manipulation should also be eligible for
8 the exception because should those products --
9 assuming those products are used for homologous
10 use in the same surgical procedure, to regulate
11 them not under 361; to regulate them under 351 --
12 I mean, to regulate them under 361 rather than to
13 accept them would be to impose additional controls
14 on their spread of communicable disease since
15 that's what 361 does.

16 And as I noted, there are a need for
17 additional controls on spread of communicable
18 disease within surgical procedures and so I think
19 that would be an unnecessary burden. The other
20 area is to consider because of the intrusiveness
21 of regulating in and inspecting operating rooms,
22 even for more than minimal manipulation products,

1 where they can be adequately controlled through
2 FDA regulatory control of the drug device or
3 biologic used for the manipulation. Maybe a
4 vector, maybe a growth factor, maybe a machine
5 that processes that the FDA should consider
6 applying the exception so that the cell -- the
7 HCT/P itself does not require pre-market approval,
8 but those uses of the device does, as I think that
9 would be a more efficient and effective
10 regulation.

11 DR. WITTEN: Thank you. I have a
12 question for speaker number 10. I'm sorry, I'm
13 not sure who was speaking from -- this was from
14 LifeNet Health. Whoever spoke from LifeNet
15 Health, I'm just wondering, there are comments
16 about what isn't minimal manipulation, but I'm
17 just wondering if there any examples that you can
18 provide of what you would consider minimal
19 manipulation -- more than minimal manipulation?

20 DR. MOORE: More than minimal
21 manipulation. Examples of those --

22 DR. WITTEN: Not trying to put you on

1 the spot, so --

2 DR. MOORE: Well, this is the spot.
3 It's a good place. (Laughter) That's where you
4 want to be.

5 So more the minimal manipulation, I
6 think that if you took, for example, some cellular
7 therapies and took the cells, and expanded them up
8 and -- a gentleman was saying putting a vector in
9 there or something. You know, obviously, there's
10 things you can do that would be more the minimal
11 manipulation. Again, expanding cells and treating
12 them in certain ways, I think you can cross the
13 line and that would be a particular example.

14 DR. WITTEN: Okay, thank you. Other
15 questions from the panel? Okay, well -- oh, okay
16 go ahead.

17 MR. WEINER: I just had one question for
18 Dr. Lallande, is that right?

19 DR. BRODY: (inaudible)

20 MR. WEINER: Sorry. If I understood
21 your presentation correctly, I think you were
22 focusing on minimal manipulation questions and I

1 was just curious --

2 DR. BRODY: Yes.

3 MR. WEINER: -- if you have any comments
4 on how that ties into the --

5 DR. BRODY: I'm sorry?

6 MR. WEINER: I was just curious if you
7 had any comments on how the analysis would shift
8 toward -- if you're talking about homologous use,
9 if you had any views on homologous use for stem
10 cells?

11 DR. BRODY: I'm sorry, I didn't hear
12 your question. Can you repeat again?

13 MR. WEINER: I was just curious if you
14 had any thoughts on homologous use as for --
15 seriously it might be a logical continuation from
16 what you were saying about minimal manipulation
17 for stem cell sources, if you have any comment on
18 it? If you don't, that's fine, on homologous use.
19 What would be within balance or how the two
20 connect?

21 DR. BRODY: I believe that the use of
22 this type of enzyme -- the competent DNA-derived

1 enzyme really can be used whether it's homologous
2 or non-homologous. What we like to believe is
3 that the homologous use -- the definition of
4 homologous use should be expanded because these
5 cells don't function as structural tissues per se.
6 And these cells are within fat tissue which are
7 called structural, which, in fact, are not even
8 biologically the correct terminology for their
9 purpose in the body.

10 They're only for long-term storage of
11 caloric energy in terms of biologic restriction
12 and yet we're eliminating it to the concept of
13 it's just structural tissue. But I believe it
14 plays the right role if you use the right enzyme;
15 if you use it in the right conditions, there is no
16 alteration of the biological characteristics, so
17 it would fit in those two useful categories.

18 MR. WEINER: Thank you.

19 DR. WITTEN: Okay. I have one last
20 question which is for the RTI Surgical, speaker
21 number 16, if you're still here? And this is just
22 for some clarification of your comments. And

1 thank you for coming and commenting to the guide
2 pieces. I just would like to know -- so your
3 suggestion is that the guidances clearly call out
4 sterilization methods as not more than minimally
5 manipulative. But I'm just wondering is there
6 something in the guidances that has raised this
7 question? Or are you just making a suggestion
8 that that should be included, also?

9 DR. DEURLING: It's simply a suggestion
10 that improving the specificity of the document,
11 especially for processes that are important to the
12 safety of HCT/P as sterilization processes, that
13 should be specifically called out as being
14 generally not more than minimally manipulated,
15 especially since it was already in the preamble to
16 the original rules, so just basically restating
17 it.

18 DR. WITTEN: Basically restating it.
19 Okay, thank you. Okay, well I see we're ahead of
20 time. If there are no more questions? I see
21 we're ahead of time so perhaps we can have the
22 break now. And maybe we can reconvene instead of

1 reconvening at 11:27, we convene at 11 and have --
2 oh, yes?

3 SPEAKER: Are members of the audience
4 permitted to ask questions?

5 DR. WITTEN: We are not allowing
6 questions from the public. I'm sorry.

7 SPEAKER: Okay.

8 DR. WITTEN: But if you have comments,
9 please submit them to the docket. We would be
10 interested in --

11 SPEAKER: Can we submit for tomorrow?

12 SPEAKER: Until the 27th --

13 DR. WITTEN: You can submit until the
14 27th --

15 SPEAKER: -- of September.

16 DR. WITTEN: -- of September.

17 SPEAKER: Okay.

18 DR. WITTEN: Yeah. Okay, so we'll have
19 a break. I think we'll -- oh, okay. We're going
20 to reconvene at 11:05. And we'll hear the FDA
21 presentation at that time assuming my presenter is
22 actually here.

1 SPEAKER: Yeah, he's here.

2 DR. WITTEN: Oh, good. Okay, thank you.

3 (Recess)

4 DR. WITTEN: Okay. Thank you. I'm just
5 going to introduce, as I mentioned this morning,
6 Dr. Steve Bauer, Chief of the Cell and Tissue
7 Therapy Branch in the Division of Cell and Gene
8 Therapies in the Office of Cellular Tissue and
9 Gene Therapies at the Center for Biologics,
10 Evaluation, Research. Dr. Bauer's going to
11 provide a summary from the September 8th FDA
12 workshop on Scientific Evidence in Development of
13 Human Cells, Tissues, and Cellular and
14 Tissue-based Products that are Subject to
15 Pre-Market Approval. Following his talk, we'll
16 take a break for lunch and because we're running a
17 bit early, we're going to reconvene at 1:00 from
18 the lunch break. So I want to make sure that
19 everybody knows that 1 o'clock is when we're going
20 to reconvene. Okay.

21 DR. BAUER: Thank you, Dr. Witten. On
22 September 8th, FDA convened a public workshop

1 entitled Scientific Evidence in Development of
2 HCT/Ps Subject to Pre-Market Approval. The
3 purpose of the workshop was to identify and
4 discuss scientific considerations and challenges
5 to help inform the development of cellular
6 therapies, including stem cell-based products. I
7 am going to provide a summary of the meeting and
8 present highlights of the presentations and
9 scientific discussions.

10 The invited speakers and panelists
11 represented a variety of stakeholder communities,
12 including academia, the pharmaceutical industry,
13 professional societies, and U.S. Government
14 agencies. Materials from that workshop, including
15 speaker biographies and the agenda, are available
16 on the vaccines, blood, and biologics part of the
17 FDA webpage. Transcripts will be posted there as
18 soon as they are available. And we'd like to,
19 again, thank all the workshop participants for the
20 excellent presentations and lively, informative
21 discussions.

22 We began the day with a keynote address

1 from Dr. Irv Weissman, director of the Institute
2 for Stem Cell Biology and Regenerative Medicine at
3 Stanford. He gave a keynote presentation
4 highlighting many years of academic research that
5 led to efforts to develop a stem cell-based
6 product. Dr. Weissman's talk emphasized the
7 importance of strong scientific evidence during
8 development of a cell therapy.

9 Dr. Weissman emphasized that the term
10 "stem cell" is often misused. The term is often
11 applied to mixtures of cells that are not all true
12 stem cells. A stem cell can be defined as a cell
13 that divides to replicate itself into another stem
14 cell, but also has the ability to differentiate
15 into other cell types. What many people call stem
16 cell transplants are, in fact, mixtures of cells
17 that may or may not contain true stem cells. And
18 Dr. Weissman suggested that the term "stem cell
19 treatment" be applied only to purified stem cells.

20 After his keynote address, I presented
21 FDA perspectives on scientific evidence in HCT/P
22 development. I explained the applicable

1 regulatory pathways and the scientific review
2 disciplines involved in oversight of these types
3 of products. For cell therapy, scientific
4 evidence is the key consideration at each stage of
5 product development. Gathering of scientific
6 evidence starts in the pre-clinical phase before
7 any administration to humans. At this stage,
8 scientific evidence is gathered to support safety
9 of potential human study participants and to
10 provide evidence to support the concept of how the
11 product may work.

12 Next, scientific information that tells
13 us what is in the product and shows that it is
14 free from harmful agents is gathered. If the
15 information is sufficient, the initial human
16 clinical trials can begin. If early phase 1
17 clinical trials continued to indicate product
18 safety, and phase 2 trials provide some evidence
19 that the study products are working, confirmatory
20 phase 3 human clinical trials can be conducted.
21 If well-designed, scientifically rigorous clinical
22 trials support safety and effectiveness, then the

1 product can be moved toward the market.

2 Science is the key consideration for
3 characterization of the product for evaluation of
4 pre-clinical evidence and for conduct, and
5 analysis of the clinical trials. I described some
6 of the key scientific knowledge gaps where
7 progress would facilitate development of safe and
8 effective cell therapy products. In terms of
9 product characterization, the field would benefit
10 from development of ways to measure cells that
11 predict their biological properties related to
12 clinical performance. I described an FDA
13 regulatory science research project that we call
14 the multi-potent stem cell or MSC Consortium.

15 MSCs are often called mesenchymal stem
16 cells, but they are not a pure preparation of stem
17 cells. The Consortium has shown that commonly
18 used methods to characterize MSCs do not reveal
19 the differences between MSCs grown for different
20 lengths of time or isolated from different donors.
21 The Consortium has developed quantitative methods
22 that do reveal the differences among MSC

1 preparations in some ways to characterize some
2 biological properties. These tools could improve
3 manufacturing and characterization of MSCs and
4 other cell therapy products.

5 In session two, industry and academia --
6 academic scientists presented their experiences in
7 cell therapy product development. Speakers
8 emphasized there should be a two-way flow of
9 scientific understanding that comes from
10 pre-clinical and clinical studies. This means
11 that pre- clinical and clinical experience should
12 feed back into the lab and inform manufacturing of
13 the product. Careful analysis of the pre-clinical
14 and clinical results can lead to significant
15 refinement and improvement of cell products. One
16 speaker emphasized how important it is to have a
17 sound scientific understanding of the cell
18 product. This knowledge can help assess whether
19 manufacturing changes will have a positive or
20 negative effect on the quality of the final
21 product. Several speakers emphasized that
22 understanding the mechanism of action of the

1 product can help to design better clinical trials.

2 After the two morning sessions one and
3 two, there was a panel session with speakers from
4 these sessions. The panel provided additional
5 discussion around the points I already covered and
6 also discuss two additional points. First,
7 regulatory oversight provides a critical review
8 that advances product development. Secondly,
9 panel members also emphasized that existing FDA
10 regulatory pathways including orphan designation,
11 expanded access, and others could expedite
12 clinical development.

13 In session three, which was the first
14 session of the afternoon, we heard from
15 professional societies which have an important
16 role in the development of cell-based therapies.
17 Speakers representing the International Society
18 for Stem Cell Research, ISSCR, and the
19 International Society for Cellular Therapy, ISCT,
20 provided summaries of their professional society's
21 positions on what they call unproven cell
22 therapies. Both emphasize ethical and scientific

1 concerns arising from unproven cell therapies and
2 stem cell tourism. Both societies have issued
3 guidelines which emphasize the critical importance
4 of scientific data in providing the ethical
5 framework for clinical trials.

6 The speakers pointed out that patients
7 may not always understand whether or not there is
8 scientific evidence that supports the treatments
9 they are choosing. Also, the patients may not
10 understand whether or not they are participating
11 in a clinical trial with appropriate oversight.
12 The ISSCR representative discussed the role of FDA
13 in the product development process as an important
14 collaborator who maintained balance between
15 participants, including scientists, patients,
16 academics, and industry partners. A
17 representative of the American Society of Plastic
18 Surgeons and the International Federation for
19 Adipose Therapeutics in Science stated that his
20 society provides guidance on the use of fat
21 grafting and stromal vascular fraction to its
22 members, and these groups see scientific quality

1 is important to the field.

2 In the next session, two federal
3 agencies described the support they provide in
4 development of cell therapy products in accordance
5 with their missions. A representative from the
6 Department of Defense discussed the important
7 initiatives and goals of DOD supporting
8 regenerative medicine research to benefit injured
9 members of the Armed services. A representative
10 from the National Institutes of Health discussed
11 the National Heart, Lung, and Blood Institute
12 support of translational science for regenerative
13 medicine products, including a clinical specimen
14 and data repository, a web-based small biz
15 hangout, the Partnership for Access to Clinical
16 Trials, also called PACT, and the Progenitor Cell
17 Biology Consortium and the Progenitor Cell Biology
18 Translational Consortium.

19 The final session covered topics related
20 to patient and society experience and
21 expectations. Speakers highlighted societal
22 expectations for development of novel products

1 emphasizing safety as an overarching principle and
2 the important role of informed consent. The
3 speakers noted that patient advocacy groups are
4 important, but do not necessarily represent the
5 point of view of all patients. A representative
6 from the Foundation for Fighting Blindness
7 highlighted the complexity of cell therapies for
8 treatment of blindness and the importance of
9 careful scientific characterization of various
10 types of cell products.

11 He expressed concern that some cell
12 products were not suitable or not sufficiently
13 supported by evidence for treating blindness. The
14 Foundation for Fighting Blindness recommends that
15 all clinical stem cell therapies have convincing
16 preclinical and clinical safety data for safety
17 and efficacy, as well as FDA oversight. Dr.
18 Albini, an ophthalmologist in Florida, discussed
19 outcomes in patients treated for macular
20 degeneration. Three patients with relatively
21 functional vision received bilateral injections of
22 autologous adipose-derived cells. All three

1 subsequently developed permanent vision loss in
2 both eyes. According to Dr. Albini, all three
3 patients mistakenly believed they were
4 participating in a clinical trial.

5 Dr. Miller from Brigham and Women's
6 Hospital at Harvard discussed a 66-year-old man
7 who sought treatment for lingering effects from an
8 ischemic stroke. He was reportedly given multiple
9 different stem cell injections described as
10 mesenchymal, embryonic, and fetal neural stem
11 cells. At several different commercial stem cell
12 clinics outside the U.S., he subsequently
13 developed progressive lower back pain, paraplegia,
14 and urinary incontinence. Magnetic resonance
15 imaging revealed a mass growing around his spinal
16 cord. A biopsy from this lesion indicated the
17 cells were not from his body, but came from the
18 infused cells. He then received radiation
19 therapy, which helped temporarily, but now the
20 mass is growing again.

21 After sessions three, four, and five,
22 there was a panel session with speakers from the

1 earlier sessions. Discussion addressed the
2 importance of protecting research participants,
3 the need for clinical trials to be conducted with
4 appropriate oversight and backed by sound
5 scientific data. The panel also commented that
6 the public can find a tremendous amount of
7 information regarding stem cell treatments online.
8 More should be done to make sure the online
9 information is accurate and that there is adequate
10 information for both physicians and patients.

11 This may be a role for professional
12 societies and FDA oversight. Another point was
13 that patients vary in risk aversion, so there's a
14 need to build in more respect for patient autonomy
15 while protecting patients from excessive claims.
16 All panelists agreed that the products need to be
17 safe and should be rigorously developed to
18 identify which products are effective.

19 At the end of the day, Dr. Weissman
20 summarized some of the key points from the
21 presentations and discussions. One of the key
22 themes of the workshop was the complexity of cells

1 and the importance of sound science in
2 development, manufacturing, pre-clinical studies,
3 and clinical studies of cell therapies.
4 Professional societies discussed their concern
5 regarding the use of unproven cell therapies and
6 stem cell tourism and highlighted their
7 recommendations for protecting the safety of
8 patients and for developing effective treatments.
9 Government support is key to innovation and
10 progress of regenerative medicine.

11 FDA appreciates the thoughtful
12 discussion and input from the presenters,
13 panelists, and audience members of the workshop.
14 We also thank you for your participation today.
15 So we will now break for lunch and reconvene at 1
16 p.m. Thank you.

17 (Recess)

18 DR. WITTEN: We're going to get started
19 again. I'd like to thank the speakers this
20 morning for keeping to their allotted time. And
21 for those of you who are speaking this afternoon
22 who weren't here this morning, there's a timer and

1 when it turns yellow you have a minute left to
2 wrap up your presentations. So that's how you'll
3 know that you're close to the end of your time.

4 So we're going to start this session,
5 Session Two, this afternoon with a presentation
6 from a speaker from Boston College Law School.

7 DR. CHIRBA-MARTIN: Thank you, I'm
8 MaryAnn Chirba- Martin. I'm a professor of health
9 law at Boston College Law School. I also teach
10 health law at NYU Law School, and I've taught also
11 at Harvard School of Public Health. I received my
12 doctorate in health policy and law and my master's
13 in public health, also from the Harvard School of
14 Public Health. I'm speaking as an individual
15 healthcare regulatory attorney. I do not speak on
16 behalf of Boston College, no academic would, and
17 since I've never been paid or grant funded for my
18 work in this area, I have no financial conflicts
19 of interests.

20 I appreciate the presence of all of you
21 and the extension of time to hear people discuss
22 these matters. And I also appreciate the great

1 difficulty that the agency has in regulating in
2 such a complicated area that's often ethically
3 complicated and emotionally charged. I hope
4 someday there's a larger conversation about
5 improving or revising the 351361 regulatory
6 framework, but today I'd like to focus on the
7 impact of three draft guidances on the use of
8 autologous adipose-derived stem cell therapies for
9 nonstructural purposes.

10 I'd like to discuss the homologous use
11 draft guidance, the adipose draft guidance, and
12 the minimum manipulation draft guidance.

13 In 1998, the agency issued a guidance on
14 changing general to intended use for medical
15 devices. And it explained that the purpose of
16 guidance is to enable the agency to make
17 consistent and reasonable decisions. And I'm
18 concerned as an attorney that this is not
19 happening here and that the agency's actions would
20 not survive judicial review.

21 First, the agency is required throughout
22 its regulatory actions to regulate based on a

1 product's intended use. And by refusing to
2 acknowledge the use of adipose tissues for
3 nonstructural purposes, it is essentially
4 disregarding a manufacturer's intended use in
5 violation of its statutory requirements to do so.
6 By law this would generate absolutely no deference
7 from a court under chevron analysis.

8 Even if the court were to examine these
9 actions -- and guidances can be evaluated by
10 judicial review in certain circumstances -- even
11 if they were to extend some level of deference, I
12 still think these would fail as arbitrary and
13 capricious. The draft guidances themselves
14 acknowledge that adipose serves both structural
15 and nonstructural purposes or at least they
16 include structural and nonstructural components
17 and the authorities the guidances cite in support
18 also say that that has both structural and
19 nonstructural purposes.

20 And yet the guidances go on to impose
21 this rubric of evaluating adipose therapies only
22 in terms of their structural use. This inevitably

1 makes the evaluation of minimum manipulation
2 impossible because the evaluation of minimum
3 manipulation depends on the original relevant
4 characteristics, relevant to the intended use.
5 And it forces adipose therapies to be wrung
6 through a framework of evaluating structural use
7 when the relevant characteristics are
8 nonstructural. So, at a minimum I urge this court
9 to extend the use of structural to include both
10 structural and nonstructural.

11 Then the homologous use stat, draft
12 guidance poses an additional concern with regard
13 to the ability of fat to serve structural
14 purposes. It states that fat can be used to fill
15 the hollows of a woman's cheeks, it can be used to
16 restore the shape of a woman's body, but it cannot
17 be used to reconstruct a breast. And the reason
18 is because the basic function of a breast is
19 defined as lactation and adipose does not restore
20 lactation. Restoring lactation is not a woman's
21 concern.

22 It was not the concern of the Women's

1 Health and Cancer Rights Treatment Act, which said
2 that breast reconstruction is medically necessary.
3 It is unfair and illogical and arbitrary and
4 capricious to leave a woman with few options for
5 reconstruction, most especially in a foreign
6 implant when a woman would be most unlikely to
7 tolerate it.

8 I ask this court to, at a minimum,
9 exercise enforcement discretion as it did with its
10 FMT guidance in March 2014, decide not to enforce
11 these guidances against individual practitioners
12 who are using same cell autologous adipose
13 therapies for nonstructural purposes, and explain
14 why a breast is mainly a lactation organ and
15 nothing else. Thank you. (Applause)

16 DR. WITTEN: Our next speaker is from
17 Case Western University.

18 DR. CAPLAN: Hi, my name's Arnold
19 Caplan. I'm a professor at Case Western Reserve
20 University in Cleveland. And I'm not speaking for
21 the university, I'm speaking for myself as an
22 individual.

1 In the late 1980s, I gave the term
2 "mesenchymal stem cells" to a cell which I was
3 able to isolate from bone marrow, put into
4 culture, and expand in culture. That term is
5 wrong, and I apologize for calling it a stem cell.
6 It is not a stem cell. The assumption was that
7 this cell was part of the stroma of marrow. The
8 cell is not a part of the connective tissue or
9 stroma of marrow. It is a perivascular cell. And
10 as a perivascular cell, it has a function only in
11 cases of inflammation or injury.

12 In this case, this cell comes off the
13 blood vessel and does two things. From its front
14 it secretes a curtain of molecules which stop your
15 overaggressive immune system from surveying the
16 damaged tissue behind it. And from the back of
17 the cell, it secretes a different group of factors
18 which actually allow the tissue behind it to
19 regenerate in a slow and unscarring process.
20 This, therefore, is a cell which is medicinal in
21 its function and because I have such a delicate
22 ego, I've written an article which asks my

1 colleagues to continue to use the MSC
2 nomenclature, but I've renamed this cell a
3 medicinal signaling cell. And so, therefore, when
4 I lecture I beg the audience to not use the stem
5 cell nomenclature. Having said that, I want to
6 address two points of the guidance documents.

7 Number one, everything I've just talked
8 about is paracrine activity of cells. And so I
9 would state that almost every tissue of the body
10 is itself paracrine. Fat in particular has an
11 absolutely essential paracrine activity as a
12 tissue; and so, therefore, if you transplant or
13 transfer fat from one tissue to another, you're
14 taking advantage of its paracrine activities,
15 which are not covered whatsoever, as the last
16 speaker pointed out, in your guidance documents.
17 And so, therefore, I would suggest that the
18 guidance document could be augmented by talking
19 about clinically homologous use. And so,
20 therefore, a fat transfer to my knee, to my elbow,
21 to my shoulder are all comparably clinically
22 relevant and could, therefore, produce a paracrine

1 and/or clinically relevant activity as some
2 published studies have shown. So this is
3 suggestion number one.

4 Suggestion number two is that the
5 guidance documents and the emphasis of the meeting
6 on Thursday was to try to put at rest the illegal
7 or irrational or unsupported use of cell-based
8 therapy. My suggestion in this regard would be a
9 registry. A registry which puts the -- of course,
10 protects the patient's name and identity, but puts
11 the clinical symptoms under which they're being
12 treated and outcome parameter lists, sequential
13 outcome parameters so that one could determine
14 whether a particular therapy was effective or not
15 effective. If that web, if that registry was in
16 real time on a publicly accessible website, then
17 we could determine just as patients, whether a
18 particular doctor's office was producing
19 clinically relevant results from any one of these
20 therapies. I want to state unequivocally that
21 this has been in practice for over 25 years for
22 bone marrow transplantation, which the FDA

1 supports and allows. So it seems to me that the
2 FDA likewise, in helping to make sure that
3 efficacious, clinically efficacious technologies
4 are being used, should support also a registry for
5 other cell-based therapies and/or tissue
6 transfers. It's important I think that these
7 guidance documents are based in science and in the
8 reality. And this paracrine activity is one of
9 the most important, and I, of course, will honor
10 any decision this panel will make and help enforce
11 it.

12 Thank you.

13 DR. WITTEN: Our next speaker is
14 representing the Indiana University School of
15 Medicine.

16 DR. MARCH: Hi, I'm Keith March. It's a
17 great pleasure to be here. Just as stated by the
18 prior speakers, of course, I am representing the
19 opinions that I can best offer, and I hope that
20 they're helpful. I can't actually represent the
21 entirety of the university, Indiana University.

22 My M.D. is in cardiology, expressed in

1 would like to introduce is that we consider the
2 notion of a functional homology rather than an
3 anatomically sourced homology. And just as he
4 mentioned, I think this nicely dovetails that
5 vascular and tissue support that these cells
6 naturally undertake physiologically is what
7 they're often being used for, let's say in the
8 context of skeletal or heart muscle ischemia; also
9 in the context of renal ischemia, the nervous
10 system, intestinal, and eyelet based ischemia. So
11 as you can see a wide range of topics, if you
12 will, or organs, where a target is appropriately
13 considered to be the subject of a homologous
14 function of these cells, and I think that's maybe
15 a useful concept to consider.

16 Well, all the work we've been doing with
17 the adipose stem cells led us to be very
18 interested in cell therapy trials more broadly.
19 We've had the privilege since 2012 to participate
20 as one of the seven members in the United States
21 of what's called the Cardiovascular Cell Therapy
22 Research Network, which is supported by NIH.

1 Very privileged and thankful to be one
2 of those members, and also I had the chance to be
3 the Clinical Network BSMB chair for several years
4 before we became a member of that network.

5 So as such, we've had the opportunity to
6 participate in the planning or conduct of seven
7 clinical trials involving either bone marrow or
8 SVF, stromal vascular fraction. And all of those
9 have been regulated in context with the
10 development and discussion with the FDA. And we
11 very much appreciate and have found the CBER
12 guidance and help through those discussions to be
13 enormously useful. So everything we've done is in
14 either the IDE or IND environment. And in fact,
15 we have four more that we're preparing with IDEs
16 involving SVF or other indications.

17 So from that perspective or history, I
18 would like to then move to some comments relating
19 to the draft guidances touching on SVF and ASCs.
20 The one I've already made in particular is about
21 the functional homology, and I think that relates
22 to the notion of what is a homologous use.

1 The second I'd like to make rests on a
2 thought about history and patient autonomy. Bone
3 marrow transplant is of great interest to all of
4 us and as is cord-blood transplant. Those began
5 to be developed in the '70s and '80s and as a mere
6 cardiologist, I thought it important to talk to
7 some real HEMONC colleagues. So I've talked to
8 several about this topic of bone marrow and
9 cord-blood transplantation who allowed me to cite
10 them actually.

11 Ian McNiece, who's been involved in the
12 bone marrow field for about 35 years and was a
13 director of the bone marrow transplant
14 laboratories at Johns Hopkins followed by the
15 University of Miami, followed by MD Anderson, as
16 well as Joanne Kurtzberg, who's here in the
17 audience, and Pat Lara, our home, at Indiana Cell
18 Cancer Center Director. And all of them have
19 declared that if the regulatory environment back
20 in those times were more similar to how it is now,
21 we may not in fact be able to have had the
22 opportunity to see, say, a million bone marrow and

1 cord- blood transplants have occurred, which I
2 believe was the number I saw cited in 2013, with
3 of course many of those people benefitting
4 significantly.

5 And the reason for that is that in those
6 early transplantation efforts we didn't know much
7 about HLA. And dozens, if not hundreds of people
8 died as a consequence. However, those findings
9 about HLA were in fact critical to the advancement
10 of the field.

11 And so I think a consideration about
12 risk-benefit and where we are with the bar, if you
13 will, that's placed for entry into human trial and
14 learning not only about efficacy, but also about
15 safety, needs to be considered. Some have said
16 that if in fact we were in that domain back then,
17 we may not have bone marrow transplant at all. So
18 I think we need to think about whether some kind
19 of relaxation or moderation of restriction might
20 allow more work to be conducted and offer more
21 opportunities in the United States. And I would
22 totally agree with the prior comments from Dr.

1 Caplan about the field needing a registry, such
2 that participation in clinical trials be actually
3 brought into a mandated situation so that registry
4 and data can be brought forward.

5 The last comment that I have is a
6 regulatory one, and that is, some of the clinics
7 that we are, I think, uniformly trying to regulate
8 in addition --

9 DR. WITTEN: Excuse me.

10 DR. MARCH: Yes.

11 DR. WITTEN: I just want to mention, I
12 appreciate your comments, but you need to be
13 mindful of the time limitations.

14 DR. MARCH: Okay.

15 DR. WITTEN: Okay.

16 DR. MARCH: I think then I'll take this
17 last point, and I will hold it for another
18 discussion if we want to. I think the main points
19 I brought forward as best as I can and I
20 appreciate your time. Thank you.

21 DR. WITTEN: The next speaker is from
22 Wake Forest University School of Medicine.

1 DR. ALICKSON: Hello, my name is Julie
2 Alickson and I'm the director of the Regenerative
3 Medicine Clinical Center at Wake Forest Institute
4 for Regenerative Medicine. I've been in the field
5 for about 25 years, cell therapy regenerative
6 medicine, and now lead the Clinical Center where
7 we work with cell therapies, tissue engineered
8 organs, bio-materials and devices. So I've been
9 pre and post good tissue practice regulations and
10 I'd like to comment on two of the guidance
11 documents. I'd also like to thank FDA for
12 allowing me to speak in a public forum and along
13 with all the others to be able to help to form the
14 final guidance documents that you're working on.

15 So I'd like to comment on the guidance
16 documents that are associated with the 1271
17 homologous use of human cells, tissues, and cell
18 and tissue-based products that was published in
19 October of 2015. And it starts out by the first
20 question, what is the definition of homologous
21 use? And so I'm just going to kind of lead you.
22 I have a couple comments and recommendations for

1 this guidance document, and so it talks about
2 homologous use means repair, reconstruction,
3 replacement, supplement of the recipient cells and
4 tissues with an HCT/P that performs the same basic
5 function, including cells or tissues. And we're
6 talking about the cells that are identical, either
7 to the donor cells and tissues or the recipient
8 cells that may not be identical to the donor.

9 They go back with number three talking
10 about the same basic function in the definition of
11 homologous use, the same basic functions
12 considered to be those basic functions of the
13 HCT/P that performs in the body of the donor,
14 which when transplanted, implanted, infused,
15 transferred would be expected to perform in the
16 recipient. The recipient to perform all basic
17 functions, it performs in the donor in order to
18 meet the definition of homologous use.

19 However, to meet the definition of
20 homologous use, any of the basic functions that
21 the HCT/P is expected to perform in the recipient
22 must be a basic function that the HCT/P performs

1 in the donor. So the draft guidance goes on to
2 talk about several different examples that then
3 can be either homologous or non-homologous use,
4 and I'm looking at 3.4, the basic functions of
5 amniotic membrane, including covering, protecting,
6 saving as a selective barrier for the movement of
7 nutrients between the external and in utero
8 environment.

9 Amniotic membrane is use, they give the
10 example of bone tissue replacement and they are
11 saying that this is not homologous use, which I
12 agree with, but I'd like to recommend and offer my
13 comments that possibly they include when amniotic
14 membrane is used as a selective barrier to retain
15 fluid, potentially over wounds or some other
16 environment that it could be considered a
17 homologous product.

18 The other guidance I'd like to comment
19 on is minimal manipulation of human cells,
20 tissues, and cell-based products. And this talks
21 about the definition of minimal manipulation --
22 sorry, the minimal manipulation talking about

1 structural tissue. And it means that the HCT/P
2 does not alter the original relevant
3 characteristics of the tissue relating to utility,
4 and for cells that the minimal manipulation does
5 not alter relative biological characteristics.

6 If you go down to example 7.1 of the
7 amniotic membrane, original relevant
8 characteristics of the amniotic membrane serve as
9 a barrier generally for the tissues physical
10 integrity, tensile strength, and elasticity. So
11 there's two examples under there, and I'd like to
12 recommend that there be a third example.

13 The first example talks about a minimal
14 manipulation of the amniotic membrane that's
15 mechanically and chemically processed as a
16 decellularized amniotic membrane. The second
17 example talks about the manufacturer grinds and
18 lyophilizes the amniotic membrane and packages
19 that as a powder, and this is more than minimally
20 manipulated. I'd like to offer an in-between
21 comment, and if we could put another example in
22 there that the manufacturer that only lyophilizes

1 and freeze dries that amniotic membrane and
2 packages it as sections to maintain that
3 structural integrity is considered minimally
4 manipulated as the dehydration process is just
5 preserving that tissue. And it would be, if it's
6 used as a membranous barrier such as it's used as
7 the amniotic membrane.

8 I'd also like to say that regenerative
9 medicine is a game-changer, so I'm hoping that
10 we'll have the opportunity to move some of these
11 lower risk products forward for people and their
12 attention. I'd like to thank the FDA in allowing
13 us to speak, and thank you.

14 DR. WITTEN: Thank you. Our next
15 speaker is from Alston & Bird.

16 MR. SCHEINESON: Good afternoon.
17 Forgive me for reading this, but five minutes
18 isn't a very long time. Thank you for the
19 opportunity to speak directly to my former FDA
20 colleagues concerning these guidance documents. I
21 understand this is a bit of a marathon for
22 everyone. Detailed comments will be submitted

1 electronically with legal authorities.

2 My name is Mark Scheineson. I head the
3 Food and Drug Practice in the Washington office of
4 Alston & Bird. As a practicing FDA lawyer for
5 over 35 years and a former FDA associate
6 commissioner, I've worked with dozens of clients
7 on constructive ideas to help advance medical
8 innovation. I also represent the bipartisan
9 policy center, which will speak in session three
10 in its panel of cell therapy experts.

11 Together, they seek to modernize the
12 Food, Drug, and Cosmetic Act to create a practical
13 statutory pathway tailored to the unique
14 attributes of cells and tissue-based therapies
15 rather than relying exclusively on the patchwork
16 of regulations and guidance. Because I've only
17 five minutes to speak, probably now four, I will
18 get directly to the point and will likely speak
19 way too fast.

20 From the perspective of clarifying the
21 agency's discretion or ambiguity in its
22 application of terms used in 1271 and promoting

1 consistency, the draft guidance is welcome and
2 appreciated. However, my colleagues and I believe
3 that these guidances miss an opportunity to
4 recognize the revolution in cell therapy that
5 surrounds us.

6 While none of the speakers want to
7 sanction quackery, there are unsafe clinical
8 practices. FDA adopted language and examples that
9 are even more conservative and restrictive than
10 its actual application of these rules in review of
11 existing products.

12 This might have been okay in 2001, when
13 the 1271 rules were initially promulgated, but not
14 in 2016, when the entire world has taken notice
15 and expedited use of regenerative characteristics
16 of patient cells based on thousands of published
17 clinical studies. It is also not okay because of
18 the existing regulatory paradigm, where if narrow
19 cell or tissue use is not regulated by 1271, these
20 uses are thrown across a Grand Canyon into the BLA
21 or PMA drug and device delivery pathway. As you
22 know best, that pathway takes an average of 12 to

1 15 years of development time and 200 million to a
2 billion dollars in financial resources. Our top
3 three suggestions to revise these draft guidances
4 in the finals are these.

5 Number one, please don't ignore the
6 discretion and regulatory tools you possess to
7 foster innovation while protecting patients.
8 These guidance documents all slam the door shut on
9 the use of stem cells, which even in the narrow
10 circumstances need to proliferate and
11 differentiate to work.

12 Just as a generation of hemopoietic stem
13 cells from cord blood have eliminated the need to
14 extract bone marrow matches in treating blood
15 cancers, why shouldn't panelists have the right to
16 use their own stem cells for simple, orthopedic or
17 cosmetic uses now if responsible, registered and
18 licensed clinics observe all the protections
19 inherent to 1271?

20 Number two, guidances are the most
21 helpful if they contain specific examples, but the
22 examples in these guidances are the most narrow

1 possible: homogenous skin grafts, heart valve
2 replacements. My practice has, for example, seen
3 FDA allow use of amniotic tissue to treat corneal
4 erosion in the eyes as homologous under 1271 and
5 other far more reaching examples. Why can't these
6 types of cutting-edge examples be included in
7 these guidances?

8 Third and last, most alarming is that
9 FDA proposes to artificially limit the use of
10 adipose stem cells and many others by reference to
11 the underlying characteristics of the tissue in
12 which those cells are located. Examples,
13 structural support or padding and cushioning
14 against shock in fat tissue. This approach
15 minimizes the tools FDA gave itself in the plain
16 language of 1271.3(f)(2), definition of minimal
17 manipulation.

18 Cell manipulation as defined in a
19 section of the regulation separate from structural
20 tissue is allowing processing that does not alter
21 the relevant biological characteristics of the
22 cells themselves. FDA inextricably adds to the

1 cells the unrelated requirements of structural
2 tissue in 1271(f)(1), where the processing can't
3 alter the tissue's utility for reconstruction,
4 repair, or replacement. If the product is a cell
5 itself and not a cellular tissue and the cells
6 possess the biological characteristics to divide
7 and differentiate, it should be irrelevant that
8 the cells were found in (inaudible) tissue and
9 violate the regulation.

10 Formal written comments will include
11 many other constructive suggestions. The
12 regulated community needs bright lines. Thank you
13 for your continued assistance.

14 DR. WITTEN: Thank you. Our next
15 speaker represents Navigant Consulting.

16 DR. O'SHEA: Thanks for having us here.
17 I'm Suzanne O'Shea. My comments today are based
18 on my long experience as an FDA employee dealing
19 with these issues and working in private practice
20 for the last nine years with a number of tissue
21 manufacturers. My comments are my own and do not
22 represent the views of any client or my employer.

1 And I have five quick points to make today.

2 First, the draft guidance on minimal
3 manipulation introduces the concept of main
4 function for the very first time. The concept
5 does not appear in 1271 or in any preamble to any
6 proposed or final regulation. The draft guidance
7 cites page 26749 in the preamble of the May 14,
8 1998, proposal for the assertion that the main
9 function of the HCT/P in the donor determines
10 which definition of minimal manipulation applies.
11 However, the phrase "main function" is never used
12 in the proposal. The closest phrase on 26749 is
13 "basic function or functions," which is to be used
14 in the context of determining homologous use.
15 Creation of an important new concept cannot be
16 done through guidance.

17 I request that if FDA wishes to pursue
18 the main function concept, it do so through notice
19 and comment rulemaking.

20 Two, the draft guidance on minimal
21 manipulation provides FDA's unilateral conclusions
22 on whether tissues are structural or

1 nonstructural. The guidance process does not
2 provide sufficient opportunity for industry and
3 academia to provide input into the classification
4 of tissues as structural or nonstructural. I
5 recognize that comments may be submitted to the
6 draft guidance, and I do appreciate this public
7 hearing.

8 However, FDA is under no obligation to
9 articulate a response to comments submitted to a
10 draft guidance or to explain its reasoning. I
11 request that FDA's classification of tissues as
12 structural or nonstructural be based on
13 articulated reasoning that fully takes into
14 account the views of industry and academia through
15 notice and comment rulemaking.

16 Three, the draft guidance on minimal
17 manipulation ignores the reality that some human
18 tissues have both structural and nonstructural
19 functionality in the donor. I recommend that FDA
20 expressly acknowledge the full range of
21 functionality of human tissue in the donor,
22 including the reality that some tissues have

1 structural and nonstructural functionality.

2 As a specific case in point, FDA stated
3 in a 2001 designation letter that amniotic
4 membrane has nonstructural anti-scarring,
5 anti-inflammatory functionality in the donor. FDA
6 now says in the guidance document, without any
7 explanation of why it has changed its mind, that
8 amniotic membrane is only structural. I recognize
9 that a designation letter is intended for a
10 specific product and that may not be applicable to
11 similar products. However, a scientific
12 conclusion about the functionality of a tissue in
13 the donor cannot vary based on the use of the
14 product or the tissue in the recipient.

15 Number four, the draft guidance
16 documents on homologous use explicitly relies on
17 the classification of tissue as a structural or
18 nonstructural to identify acceptable homologous
19 uses. In creating the homologous use regulations,
20 FDA considered and specifically rejected different
21 definitions of homologous use for structural and
22 nonstructural tissues. By importing the concept

1 of main function into the analysis of homologous
2 use, FDA is limiting the range of acceptable
3 homologous uses, contrary to current regulations.

4 Number five, FDA has applied the
5 definition of minimal manipulation inconsistently.
6 FDA has acknowledged that micronized bone is a
7 Section 361 product when intended for use as a
8 bone void filler, even though micronization
9 self-evidently alters the strength and
10 compressibility of bone.

11 It must, therefore, be the case that FDA
12 has concluded that the strength and
13 compressibility of bone are not relevant to the
14 bone's utility as a bone void filler. On the
15 other hand, FDA has concluded that micronized
16 amniotic membrane is more than minimally
17 manipulated when intended for anti-scarring,
18 anti-inflammatory uses because tensile strength
19 and elasticity are altered. Tensile strength and
20 elasticity are not relevant to the utility of
21 amniotic membrane for anti-scarring and
22 anti-inflammatory uses. FDA has never explained

1 this discrepancy, and I request that FDA provide a
2 scientific explanation for the difference. Thank
3 you. (Applause)

4 DR. WITTEN: Thank you. Our next
5 speaker is from OrthoKinetic Technologies.

6 DR. FERRARA: Good afternoon. I'm Dr.
7 Lisa Ferrara and I'm president of OrthoKinetic
8 Technologies and Testing Technologies, and I'm
9 here today to give my independent expert opinion
10 that tensile strength and elasticity of tissue is
11 not altered by cutting the tissue into small-sized
12 particles. My disclosure is I own OrthoKinetic
13 Technologies and Testing Technologies. They're
14 ISO certified fee-for-service companies.

15 The FDA draft guidance on minimal
16 manipulation defines minimal manipulation as
17 shown. In an example, FDA applied that definition
18 to amniotic membrane that had been micronized,
19 concluding that the micronized amniotic membrane
20 is not minimally manipulated because the
21 micronization process results in a loss of tensile
22 strength and elasticity of the original tissue

1 related to its utility to function as a physical
2 membrane.

3 OrthoKinetic Technologies was one of the
4 independent testing firms that conducted the
5 mechanical testing on multiple-sized amniotic
6 membrane samples to determine if micronization of
7 the amniotic membranes result in altered tensile
8 strength and elasticity. My purpose for being
9 here today is to discuss these results of that
10 testing and to give my independent expert opinion
11 that tensile strength and elasticity of a tissue
12 is not altered by cutting the tissue into small
13 particles.

14 Therefore, the objective of this study
15 was to independently evaluate the dependence of
16 size on the material properties of the amniotic
17 membrane. As a background and as an engineer with
18 a very strong background in tissue and test
19 development and interpretation, I've spent many
20 years testing thousands of human and animal tissue
21 samples for the assessment of both the material
22 and the structural properties.

1 For today's purposes, the main point of
2 that is that the tensile strength and elastic
3 modulus are material properties used to
4 characterize the tissue. As explained in the next
5 slide, material properties are independent of the
6 size of the tissue as size is factored into the
7 strength and elastic modulus calculations.

8 To give you an example of this, this
9 slide demonstrates how the size of the tested
10 tissue specimen is used to calculate the material
11 properties of the tissue and why material
12 properties are independent of size or
13 configuration. The material tensile strength of a
14 tissue is measured at the point of tissue failure
15 and is expressed in terms of stress. Stress is
16 proportional to the force applied for the cross
17 sectional area to which the force is applied.

18 In the first example, a hundred newton
19 force is placed across one millimeter squared area
20 across the tissue, resulting in a stress of a
21 hundred megapascals. In the second example, 200
22 newtons is placed across a 2 millimeter squared

1 area of tissue, and the stress again is a hundred
2 megapascals. The material tensile strength will
3 be the same regardless of tissue size based on
4 these basic engineering principles.

5 The same principle applies to elastic
6 modulus. The force measurement is measured in
7 stress and the deformation is measured in strain.
8 Strain is the relative change in length compared
9 to the original initial length. The elastic
10 modulus is the stress divided by this resulting
11 strain. Therefore, a change in test sample size
12 will be normalized by the results in stress and
13 compensated for by the results in strain and the
14 elastic modulus remains the same regardless of
15 size.

16 With that background I'll discuss
17 briefly the testing or the kinetic testing did on
18 the amniotic membrane tissue. The methods
19 involved obtaining samples of amniotic membrane,
20 cutting them into different widths or different
21 groups of widths. And at the time I performed the
22 tests, OrthoKinetic technologies was not aware

1 that two other independent test labs were
2 conducting the same testing in the same fashion
3 for tensile strength and elastic modulus. For
4 tensile testing the ultimate strength was measured
5 and with consistent gauge length of 15 millimeters
6 was used for each sample of different widths.
7 Each sample was pulled to failure at a consistent
8 rate and the membrane thickness was measured
9 before and at the site of failure after testing.

10 These slides show the results, not only
11 of what OrthoKinetic testing had conducted, but
12 also the other two independent test labs. The
13 upper right graph represents the results conducted
14 by OrthoKinetic testing and the other two are the
15 results from the other labs. The scatter plots
16 for all three labs were similar with respect to
17 the linear trends and scatter patterns and no
18 significant difference was noted between widths.

19 The elastic modulus was tested in the
20 same fashion and was determined from the stress
21 and result and strain of each sample. Again,
22 similar scatter plots, my apologies, similar

1 scatter plots were shown, similar linear trends,
2 and again there was no statistically different
3 between the samples for sample width and between
4 laboratories. All three found no statistically
5 different results for tensile strength and elastic
6 modulus.

7 In conclusion, the results obtained in
8 the study for all three laboratories have been
9 presented in engineering parameters that are
10 conventionally used to characterize material
11 properties. The three independent studies all
12 show there was no statistical difference in
13 tensile strength or elastic modulus, and that the
14 scatter patterns were all the same regardless of
15 size.

16 Thank you for your attention.

17 DR. WITTEN: Thank you. Our next
18 speaker is from Parenteau BioConsultants.

19 DR. YOUNG: Good afternoon. I am Dr.
20 Janet Hardin-Young, co-founder of Parenteau
21 BioConsultants, which provides scientific and
22 regulatory consulting services with a focus on

1 cell-based therapies. I appreciate the
2 opportunity to address certain important issues
3 raised by the draft guidance documents under
4 discussion, which will potentially provide much
5 needed regulatory clarity in a space that has
6 previously received insufficient attention.

7 I will focus my remarks on the concept
8 of intended use. As a threshold matter, the
9 purpose of agency guidance is to clarify existing
10 regulation and FDA cannot and should not introduce
11 new regulations via guidance. Despite objection
12 to the various ways the guidances incorporate the
13 concept of intended use it is, of course, not new.

14 The regulatory status of virtually every
15 product under FDA's jurisdiction turns on the use
16 for which its distributor intends it. In the
17 concept of HTC/P specifically, the idea that the
18 degree of regulation to which a tissue is subject
19 would turn on its intended use has always been a
20 bedrock principle of the risk-based approach that
21 underpins Part 1271. Section 1271.10 incorporates
22 the concept of intended use most notably in the

1 requirement that Section 361 HTC/Ps must be
2 intended for homologous use.

3 When the regulatory scheme was
4 conceived, the rationale for this requirement was
5 that homologous use products can reasonably be
6 exempted from pre-market review because a tissue's
7 behavior for homologous use is readily
8 predictable.

9 By contrast, products not intended for
10 homologous use require pre-market review because
11 clinical trials are necessary to establish the
12 behavior of cells and tissues for each use.
13 Nevertheless, today the market is crowded with
14 products for which non-homologous unsubstantiated
15 therapeutic claims are being made but are
16 virtually unregulated.

17 A striking example is provided by skin
18 and amniotic tissues base allografts, products
19 marketed as wound treatments, where the validity
20 of most of the claims being made is far from
21 self-evident. The distributor of these products
22 typically announce that the claims are supported

1 by clinical data. However, the studies are often
2 underpowered, scientifically flawed and unlikely
3 to meet FDA standards for valid scientific
4 evidence.

5 Finalizing the draft guidance on
6 homologous use is crucial because it will clarify
7 for industry what is and is not permissible in the
8 Section 361 HTC/Ps and will after, also, make
9 enforcement more straightforward.

10 Historically, FDA has applied the
11 concept of intended use in the minimal
12 manipulation context. Finding that a particular
13 process may be minimal for a tissue that is
14 intended for one use, but not minimal for a tissue
15 when it is intended for a different use. The
16 minimal manipulation guidance has been criticized
17 for introducing the supposed new concept of main
18 function into determinations of whether a tissue
19 is structural or nonstructural.

20 The reality is that FDA has been
21 applying this concept to minimal manipulation
22 determinations for almost 20 years. When FDA

1 proposed part 1271, the agency stated, "FDA
2 recognizes some products may have both systemic
3 and structural effects, but intends that a
4 product's primary effect to be determinative."

5 The term "main function" may use a new
6 word, "main," instead of "primary," but the
7 concept is well established and from my
8 perspective makes a great deal of sense. For
9 example, in the context of wound healing where
10 allografts are promoted for the ability to improve
11 the speed and quality of healing by interacting
12 with the wound at the cellular level, the
13 potential impact of various processes, processing
14 techniques is much greater than the impact of
15 these same processes when the tissue is intended
16 as a wound covering which is merely a physical
17 function.

18 In conclusion, I'd like to emphasize
19 that wound healing products are targeted at a
20 particularly vulnerable, chronically ill
21 population. I'd like to urge the agency to move
22 quickly to finalize the guidances, retaining an

1 approach that protects the public health and
2 encourages innovation by providing meaningful
3 clarity to the boundaries set forth in Section
4 1271.10.

5 DR. WITTEN: Thank you. Our next
6 speaker is from the California Stem Cell Treatment
7 Center and Cell Surgical Network.

8 DR. LANDER: Thank you very much. I'm
9 Dr. Elliot Lander. I'm a urologic surgeon,
10 co-founder and co-medical director of the Cell
11 Surgical Network. The Cell Surgical Network
12 represents over 400 physicians participating in
13 nearly 100 multidisciplinary affiliated clinics in
14 the U.S and around the world. Since 2010, CSN
15 affiliates have performed over 5,000 procedures
16 under IRB protocols using our standardized
17 same-day cell surgical procedure with autologous
18 SVF.

19 Our patients receive proper preoperative
20 IRB informed consents and afterwards safety and
21 efficacy data is collected online. Our data has
22 been submitted for peer review publication and

1 also to the FDA. It is safe. There have been no
2 deaths, infections, emboli, or any severe adverse
3 events related to cell therapy. It works and
4 improves many conditions where cellular repair is
5 necessary.

6 While collecting investigative data, we
7 provide cell therapy for our patients in a
8 low-risk, cost-effective, and transparent
9 investigational manner. Often at reduced rates,
10 even for free, we're making regenerative medicine
11 available to Americans today through our SVF
12 outpatient procedures while we continue to gather
13 data helping us to improve and advance patient
14 care. This is the reason we became physicians.

15 While statements are frequently made
16 claiming that such cell therapies are not FDA
17 approved nor such clinics performing them
18 regulated, let us remember that the practice of
19 medicine is already heavily regulated by state
20 medical boards, hospital peer review committees,
21 plaintiffs' attorneys, and malpractice carriers.

22 But these regulations we address today

1 were born out of a congressional mandate to the
2 FDA to prevent the introduction, transmission, and
3 spread of communicable disease. With jurisdiction
4 over drugs and devices, the FDA has now tried to
5 define when our body parts come under their
6 authority by considering federal rules based on
7 fat being only a cushion, disregarding the science
8 of what we know about fat.

9 Technically, with the contemplated rules
10 the FDA would have broad sweeping jurisdiction
11 over many traditional surgical procedures that
12 don't strictly follow the new guidelines. We
13 support guidelines giving the FDA the proper
14 authority to ensure that we do not risk
15 introduction of communicable disease from outside
16 sources. However, rules should not be used to
17 infringe on a patient's right to surgical options
18 using their own autologous tissue. Do we really
19 want artificial and scientifically arbitrary
20 guidance rules to dictate the course of any
21 surgical procedures that violate the proposed list
22 of exemptions?

1 To date there has never been an
2 FDA-approved surgical procedure. Further,
3 same-day surgical procedures providing autologous
4 cell therapies by their very nature are not fully
5 closed systems and they can never be held to the
6 same standards as a pharmacologically produced
7 product.

8 Medicine has historically been advanced
9 by the wise tradition of allowing physicians to
10 use any FDA- approved drugs and devices in any way
11 they see fit to advance innovation and help their
12 patients. While some oversight might be prudent,
13 guidance document language should be reasonably
14 flexible for physicians and their patients,
15 doctors should avoid irresponsible advertising and
16 labeling claims not supported by data. And state
17 medical boards and a variety of agencies are
18 already in place to counter deceptive advertising.

19 CSN has endeavored to provide a
20 transparent platform to gather real data. Our
21 database registry system can be recapitulated or
22 licensed by regulators as a model for the ethical

1 advancement of regenerative medicine. Reputable
2 clinics will be able to easily comply with the
3 registration process. Such transparency would
4 only serve the public by helping us advance
5 protocols that work, eliminate ones that don't,
6 paving a path for more controlled clinical and
7 laboratory validation studies in the future, but
8 creating artificial and contrived rules that
9 impact an entire nascent field of autologous SVF
10 therapy will have unintended adverse consequences
11 that will have epic ramifications. The FDA will
12 be inadvertently selecting technology winners and
13 losers that have little to do with safety and
14 efficacy and more to do with the semantics of
15 guidelines proposals.

16 The FDA will be complicit in
17 criminalizing certain practices of medicine that
18 are greatly supported by the American public,
19 despite a recent smear campaign intended to
20 marginalize a new way of healing patients. Every
21 day our network team and the hundreds of doctors
22 we do research with in the U.S and around the

1 world are seeing things that we were told were
2 impossible in medical school. If this wasn't real
3 and safe, we'd all go back to our previously
4 successful practices, and autologous cell therapy
5 would just simply fade away. Clearly that's not
6 the case. Let patients and doctors decide. Let
7 not special interests attempt to manipulate our
8 distinguished regulatory agencies under the guide
9 of protecting society. Thank you very much.

10 (Applause)

11 DR. WITTEN: Thank you. Our next
12 speaker represents Celebration Stem Cell Center.

13 DR. BADOWSKI: Thank you for allowing me
14 to address the panel today. My name is Michael
15 Badowski. I'm a researcher who has, among other
16 things, been working on the cells and tissues of
17 today's topics since 1999. I currently serve as
18 laboratory director of Celebration Stem Cell
19 Center in Arizona, involved in cord blood stem
20 cells and adipose tissue cryopreservation and as
21 operational director of the University of Arizona
22 Health Sciences Bio Repository.

1 As a researcher and a businessman
2 involved in the use of human cells and tissues and
3 on behalf of Celebration Stem Cell Center, we
4 respectfully submit to the FDA to reconsider
5 several points published in previous draft
6 guidelines. We hope that, one, the FDA would
7 broaden the definition of adipose tissue to
8 include structural and nonstructural uses to
9 better reflect the variety of effective clinical
10 applications; two, allow the nonstructural use
11 definition to more clearly determine homologous
12 use; and three, refine and clarify the same
13 surgical procedure exception.

14 Currently, the FDA utilizes the terms
15 structural and nonstructural under 1271.10(a). It
16 would support better outcomes for more clinicians
17 and researchers if adipose tissue was not
18 cataloged merely as structural. Changing the
19 classification of adipose tissue to include both
20 structural and nonstructural purposes would more
21 accurately account for the intended use. And this
22 concept of intended use is at the heart of the

1 rules that we would hope the FDA to adopt in
2 regard to adipose tissue specifically in HCT/Ps in
3 general. Adipose tissue can be defined as
4 connective tissue consisting of a variety of cell
5 types performing a variety of functions.

6 But because it's connective tissue in
7 general, it provides support and structure to the
8 body, FDA currently considers connective tissue
9 including adipose tissue to be solely structural.
10 Currently the many nonstructural functions have
11 thus far been not sufficiently addressed.

12 Some examples for your consideration
13 are: adipose tissue has critical function of
14 energy storage which is not a structural function.
15 More specifically, brown fat not only stores
16 energy, but has an important role in using these
17 stores in regulation of body temperature.
18 Adipocytes store triglycerides and lipoproteins.
19 These are critical chemical feed stocks for
20 synthesis of cells in general and largely apply to
21 erythropoiesis.

22 Important precursors such as forms of

1 cholesterol are also stored in adipocytes. Proper
2 levels of these molecules have a profound effect
3 on hematopoiesis. A great many adipokines are
4 produced in the adipose tissue making it an
5 important paracrine and endocrine organ. And
6 perhaps most importantly, adipose-derived
7 mesenchymal stromal cells have shown to be an
8 important player in wound healing. All these
9 examples are well known to the community and are
10 all nonstructural. Furthermore, keeping adipose
11 tissue listed solely as structural, make both the
12 determination of homologous use and determination
13 of the same surgical procedure more difficult.

14 Currently, the definition of homologous
15 use requires that the tissues serve the same basic
16 function in the recipient as in the donor.
17 However, as I've just listed many nonstructural
18 uses, they would not only apply for the homologous
19 use exception because adipose is still defined as
20 structural.

21 This is problematic because the use
22 would fit all other qualifying descriptions as

1 homologous. The FDA has previously stated as part
2 of the same surgical procedure exception that
3 HCT/Ps remain in their original form. However,
4 the Q&A published in October 2014, and other
5 statements by the FDA leave ambiguity regarding
6 the original form of HCT/Ps.

7 One might begin the conversation
8 regarding HCT/Ps by acknowledging that there are
9 three different things being discussed in that
10 very title. One, human cells, human tissues, and
11 three, products created from cells or tissues.
12 And therein lies the potential ambiguity. There
13 is a very big difference between the original form
14 of a tissue and the original form of cells. The
15 ambiguity is more pronounced when we consider the
16 multiple cell types in something like adipose
17 tissue.

18 In removal of adipose for adipose
19 transfer, the tissue would be washed. This
20 process is designed to remove blood, cellular
21 debris, and liquid oils from disrupted cells. The
22 very process of harvest will, of course, effect

1 changes to the tissue and cells. However, the
2 vast majority of individual cells are affected
3 minimally or not at all. Conversely, the tissue
4 as a whole is changed more so. One coherent piece
5 of adipose residing in an area of the body becomes
6 a collection of adipose fragments having traveled
7 through a three millimeter cannula.

8 To be able to move the adipose tissue
9 and cells from one place to another for adipose
10 transfer, one can break down the tissue with a
11 scalpel, or one could break it down with a suction
12 device. These mechanical procedures both yield
13 adipose tissue as more useable at the donor site
14 with the difference being largely in size and
15 shape. The difference in size and shape being
16 allowed under the same surgical procedure
17 exception, what then is the difference using
18 additional mechanical means to further the size
19 and shape of small adipose particles into the
20 stromal vascular fraction.

21 Unless this is addressed and clarified,
22 it remains difficult from a legal and regulatory

1 standpoint even though the procedure is
2 scientifically and medically well-founded and does
3 not increase the risk of communicable disease any
4 more than those typically associated with surgery.
5 Thank you.

6 DR. WITTEN: Thank you. Next is the
7 Long Island Plastic Surgical Group.

8 DR. DAVENPORT: Hi, my name is Tom
9 Davenport. I'm a plastic surgeon at Long Island
10 Plastic Surgical Group. I'm on staff at
11 Stoneybrook University Medical School, but I'm not
12 here representing that institution. I am here,
13 however, representing patients who have benefited
14 from dehydrated human amniotic chorionic membrane
15 products.

16 I first also wish to apologize. A lot
17 of the pictures I'm going to show are graphic, but
18 I think it's important that there are patients who
19 are really benefited and there are very few
20 products which I have found to be as useful.

21 I come from a very, very large group of
22 23 plastic surgeons, and I get referrals from 23

1 other plastic surgeons, basically cases they don't
2 want to take care of or they can't take care of.
3 It's a very unusual practice. We have five wound
4 care centers. We have 30 hospitals, and 23
5 surgeons.

6 I asked my PA to pick a slide which
7 describes our practice, and he picked this slide.
8 I'm a microsurgeon, so if you get your hand cut
9 off, I put it back on. I also do procedures.
10 This is a 12-hour procedure where I did a lateral
11 thigh flap to reconstruct someone's ankle, and
12 this is what it looks like. But not every patient
13 can have a 12- hour procedure.

14 So my motivation is purely selfish
15 reasons here. I look at the use of amniotic
16 membrane as a big part of my practice. And in
17 terms of healing patients, it's very, very
18 important. The two patients I'm going to show
19 here today actually wanted to come today, but I
20 told them I would come and represent them for this
21 purpose of this talk.

22 So this is my practice. It's entirely

1 getting out of Dodge in many situations. You have
2 all these referring doctors, they send to me for a
3 free flap.

4 My first patient, 84-year-old male,
5 ankle wound. And by the way, we've treated over
6 150 patients with these or similar products.
7 Patient has peripheral vascular disease, diabetes,
8 pyoderma, renal transplant, renal failure, and
9 he's been on steroids for 25 years. He has
10 pyoderma. He also has this other wound -- this is
11 not why I'm here -- and he has this ankle wound.
12 The patient came to me because it was recommended
13 he get an amputation. The patient is not even in
14 a condition to get a haircut, let alone a 12-hour
15 free flap.

16 This patient also was treated on his
17 pyoderma wounds and the wound healed up. We did a
18 skin graft and this patient was able to have a
19 limb salvaged and not get an amputation. His
20 pyoderma wounds also healed up as well.

21 This is another patient, 50-year-old
22 patient with Wegener's. He had a neck wound for

1 two years, failed dressing, sent to me for a free
2 flap. This patient came, had this neck wound. We
3 tried skin grafting it and the skin graft at first
4 took and then the wound kept getting larger and
5 larger. As time went on, the skin graft melted
6 away. We skin grafted again. It continued to
7 melt away. He eventually had exposed carotid
8 artery, was failure -- was having something called
9 a carotid blowout, which is fatal if it does
10 happen, especially in a 50-year-old.

11 I then called the institution that the
12 patient was sent to us by. I'm not going to
13 mention any names, but the initials are Johns
14 Hopkins, not far from here.

15 We were able to salvage this patient by
16 putting him on massive, massive doses of steroids
17 and basically treating him like a bone marrow
18 transplant patient. These are all just pictures
19 of his carotid, and we were able to salvage.

20 He then went and wanted to get his ear
21 reconstructed after we managed to salvage the
22 patient. He went to another physician where he

1 had the free flap done, and he developed this
2 wound where he would develop a pyelinital cyst.
3 It was not a pyelinital cyst. It was a recurrence
4 of his pyoderma in a worse area. So I tried
5 dehydrated human amnion chorion matrix. It healed
6 up in three treatments.

7 The patient then went back to the other
8 institution, and when they did the second stage,
9 his pyoderma came back in his neck. He was
10 treated at the other institution for about nine
11 months. After one treatment, the product called
12 Epifix, it healed with one treatment. And this is
13 a patient, again, nine months of steroids,
14 Methotrexate, and several other autoimmune
15 treatments.

16 So in closing, it's a very important
17 product in my practice. And I know we're talking
18 about all of these other different issues with
19 regulatory issues, but I think it's important that
20 we really keep the patients in mind and keep the
21 importance that some of these products really have
22 a huge impact on patients' lives. Thank you.

1 DR. WITTEN: Thank you very much. Our
2 next speaker is from the National Spine and Pain
3 Centers.

4 DR. FRIEDLIS: Hi, my name is Mayo
5 Friedlis. I'm medical director at National Spine
6 and Pain Centers. I'm here on behalf of my
7 patients, though, not on behalf of that
8 organization. I'm an interventional pain
9 physician, and much of my practice today deals
10 with regenerative treatments to deal with
11 musculoskeletal problems that didn't have good
12 solutions with what we had available. So it's on
13 behalf of those patients that I am testifying
14 today. Thank you for allowing us to testify and
15 make statements to help you with your guidance.

16 As a practicing physician, the things
17 that I think need to be discussed are bone marrow
18 aspirate. It's quickly becoming a standard of
19 care for many projects. Many treatments in
20 orthopedics is bone marrow aspirate safe. And
21 what does "homologous use" mean for bone marrow
22 concentrate? That's where I want to focus my

1 discussion today.

2 The current use of -- well, let's go to
3 this one. What can bone marrow concentrate offer
4 for musculoskeletal pain, which is my area of
5 concentration? First of all, it's an extremely
6 low toxicity. There's been no recorded case of
7 allergic or allergy rejection, no recorded case of
8 other adverse tissue growth, no recorded case of
9 cancers. High safety margin in a study of over
10 2,300 patients receiving same day bone marrow
11 aspirate. The adverse event occurrence was .5
12 percent. That's compared to 6 percent on a total
13 knee replacement.

14 So it's also safer than steroid use,
15 surgical intervention or management with opioids.
16 Much more cost-effective than other available
17 options. More effective for many conditions, such
18 as rotator cuff tears, ACL repairs, lateral
19 epicondylitis, early osteoarthritis, and others.
20 Additionally, it can slow the progress of the
21 catabolic demise of joint degeneration. In our
22 country we are seeing a younger and younger age

1 group getting osteoarthritis of the knees and hips
2 in their 40s and 50s. These don't have good
3 solutions because a replacement only lasts 15 to
4 18 years, which means they're going to have to
5 have more than one in their lifetime.

6 Replacements offer a whole higher level
7 of risk. There's reasonable proof of efficacy for
8 these procedures. More, in fact, than in many
9 orthopedic procedures currently done.

10 So what is homologous use for bone
11 marrow concentrate? The assumption is that
12 mesenchymal stem cells are somehow trapped in the
13 bone marrow and maybe they go into the circulation
14 and that they're somehow not involved in the
15 healing of other tissues. There is evidence to
16 show that they are in fact involved in the healing
17 of cartilage repair, muscle repair, tendon repair,
18 and bone repair.

19 We know this from, in the case of
20 cartilage, from the procedures called
21 microfracture, where the cartilage is in fact
22 drilled into to get the bone marrow concentrate,

1 the stem cells if you will, up from the bone
2 marrow to help heal the cartilage, which in fact
3 they do to a degree with highland type cartilage.
4 And we also know that the level of healing is
5 dependent on the number of mesenchymal stem cells,
6 that we can actually increase this healing by
7 adding mesenchymal stem cells to the surface.

8 In muscles, which are usually healed by
9 stem cells right next to them called "satellite
10 cells," we know that when those are depleted,
11 they'll just grab mesenchymal cells from the
12 circulation which are right nearby and they will
13 be healed with those.

14 Bone marrow concentrate -- or bone
15 marrow mesenchymal stem cells, that is, are shown
16 to be extremely important for tendon repair in
17 rotator cuff at the ligament/tendon level, and
18 also in bone.

19 In conclusion, let me just say that the
20 use of bone marrow aspirate is important for the
21 treatment of musculoskeletal problems. There is
22 absolutely no evidence of any dangers in using

1 mesenchymal stem cells for treating painful
2 conditions in the musculoskeletal system. There
3 is no evidence of increased risk to the public
4 using bone marrow aspirate for the treatment of
5 orthopedic musculoskeletal injuries or
6 degeneration. Bone marrow aspirate is in fact
7 safer than other alternatives, such as steroids,
8 surgery, and opioids. The treatment of cartilage,
9 bone, ligament, muscle, all represent homologous
10 use of bone marrow aspirate. The loss of these
11 treatments will reduce the quality of care
12 available to the public.

13 Thank you.

14 DR. WITTEN: Thank you. We're now going
15 to take questions from our panel to the speakers.
16 And then we will start on the next session,
17 Session 3, of several of the speakers, but take a
18 break before we ask questions of that set of
19 speakers.

20 So I'd like to start. I have a question
21 for Keith March, if he's still here.

22 First, I would like to thank all the

1 speakers for their presentations. I think it is
2 helpful to hear everyone's perspective.

3 So, Dr. March, I'm not trying to put you
4 on the spot like I did inadvertently with the
5 other speaker this morning, but one thing that's
6 always helpful for us when we write guidance
7 documents is to have examples and examples of
8 something that fits into a certain principle and
9 examples of things where the principles -- it
10 would not fit within what's described by the
11 principles. So you proposed a concept of thinking
12 about functional homology.

13 And Dr. Caplan, I want you to start
14 thinking about this question, too, because I'm
15 going to be asking you right after I finish with
16 Dr. March.

17 I just would be interested to hear if
18 you could just provide some examples of things
19 that you thought demonstrated or fit within this
20 concept of functional homology and some examples
21 where you thought that that criteria was not met.

22 DR. MARCH: Okay, I'll --

1 DR. WITTEN: And your idea. I mean,
2 your idea of this.

3 DR. MARCH: Yeah, I'll do my best. So
4 an example of a functional homology would be if we
5 take the mesenchymal stem cells from the adipose
6 tissue, also known as adipose stem or stromal or
7 secretory cells, and we put them with endothelial
8 cells from any of a variety of sources in vitro or
9 in vivo. Those two cell types can work together
10 to form -- the two evolve to form a neovasculature
11 and it's clearly a case of adult vasculogenesis
12 going on. You can do that whether it's with
13 adipose stem cells or with the mesenchymal stem
14 cells from bone marrow or a host of other sources.

15 Conversely, you can take the adipose
16 stem or stromal cells and do that with endothelium
17 that comes from the skeletal muscle, that comes
18 from the heart, coronary microvascular, or
19 macrovascular endothelium that comes from the
20 lung. And we've published and many others have
21 also published these kinds of results.

22 So the point is that that would be one

1 example of where these cells are functioning to
2 engage in and permit a two-cell based
3 vasculogenesis. And it doesn't really matter
4 which organ their partner cell, the endothelial
5 cell, is coming from, it still does the same sort
6 of thing. That's on the vascular network side.

7 Another example which has been
8 emphasized by several is the paracrine property in
9 the sense of perhaps parenchymal rescue. So not
10 necessarily only considering the support of the
11 vasculature, which Dr. Caplan elegantly pointed
12 out, is that's the one side of the perivascular
13 cell quite literally, the luminal side. But the
14 abluminal side, the side that faces out from the
15 blood vessel is useful in supporting and
16 modulating both survival and in modulating the
17 inflammatory response that's going on in the
18 parenchymal side of the organ.

19 And so we have a number of assays for
20 that. Again, both in vitro and in vivo. You can
21 take the adipose stem or stromal cell and place it
22 in a transwell membrane assay.

1 Let's take in vitro first and place it
2 above or not far from but still in communication
3 with through the media some other cell type. And
4 this other cell type could be a myocardial cell.
5 It could be a neural cell. It could be a
6 pulmonary epithelial or endothelial cell. We've
7 tried all of these and quite a few others in fact.
8 And in each case you will find a very
9 antiapoptotic effect in the context of stresses,
10 whether inflammatory or reactive oxygen species
11 mediated. And it doesn't matter which organ's
12 parenchyma that you're looking at the cell effect
13 of the ASC's as they secrete across this membrane.
14 In every case you see a very parallel rescue and a
15 turndown of the stress responses that ultimately
16 can lead to apoptosis or necrotic death of the
17 other cell.

18 Similarly, when we provide the ASC's in
19 vivo in a variety of either ischemic or
20 inflammatory situations, organ by organ, we see a
21 similar response.

22 So those would be the two that I would

1 really call into mind. The functional homology
2 that occurs when you're supporting the blood
3 vessel, the vascular side. And the functional
4 homology that occurs when you're modulating,
5 usually down modulating, the inflammatory and the
6 stress response on the parenchymal side of the
7 organ. And those would be shared whether you're
8 dealing with an ASC or an MSC. It just happens
9 that it's easier to get ASC's. Sometimes I joke
10 that I had too many of them so I had to figure out
11 what to do with those guys. But everyone, even
12 thin people, can use a little bit of their
13 fatness, especially if we're talking an antilogous
14 environment, as much of this discussion has been.
15 It's much more difficult to get the MSC's from
16 bone marrow. It's much, much more difficult to
17 get it, in fact impractical, from other sources,
18 brain, intestine, a lot of places they live, but
19 you could do it. It's just that it's convenient
20 to get them out of fat. And that's what I mean by
21 the anatomy isn't really dictating the function,
22 so that's why I urge that we think about a

1 functional homology.

2 Is that helpful?

3 DR. WITTEN: Yes, thank you. Wait,
4 before you sit down, another question.

5 DR. ANATOL: So you had several
6 recommendations during your talk, and I don't
7 think you got to give your last recommendation,
8 the regulatory consideration. I was just
9 wondering if you could take a minute or two just
10 to let us know what that was.

11 DR. MARCH: Sure. What I was thinking,
12 I think this has actually been touched on by some
13 of the other speakers, I think that in many
14 instances our concern as a collective community is
15 to ensure that the general principles of good
16 clinical practice are being followed and that good
17 facilities are the ones in which the products are
18 being delivered. So as distinct from talking only
19 about the product, as in one part of my discussion
20 I urged us to consider more liberal consideration
21 for some of the products. But I think that could
22 be balanced by a more careful vision into the

1 facilities. And so just as there is the domain of
2 HCT-type registration, I think that we could
3 consider that in a good clinical practice paradigm
4 with facilities that are doing these kinds of
5 procedures. And that might be an appropriate
6 balance whereby a facility is registered and
7 perhaps the practitioners there are registered.

8 Now, in fact, I think that the FACT, the
9 F-A-C-T, the Foundation for Accreditation of
10 Cellular Therapy, as well as the ABB, have engaged
11 in some of these kinds of things in the past. But
12 I was wondering if perhaps stepping back and
13 considering from the FDA perspective the notion
14 that facilities and their practitioners may be
15 able to be held to particular standards so we can
16 obviate, for lack of a better term, the sort of
17 strip mall concept but promote and promulgate the
18 appropriate and the best sense human trials and
19 experimentation in a registry format that occurs
20 in the context of centers which are well known to
21 be excellent in all their aspects.

22 I have some other things that have

1 little numbers on them, but I don't want to make
2 myself say the wrong numbers of .10 and .15, so I
3 will submit that in a subsequent comment. But it
4 enlarges a bit on what I've just said.

5 DR. WITTEN: Okay, thank you. Dr.
6 Caplan?

7 DR. CAPLAN: I'd just like to make one
8 point, that there are published papers on MSC-like
9 cells from a variety of sources from fat, from
10 liver, from heart, from kidney, from marrow, where
11 the transcriptomes of those cells in culture are
12 -- been analyzed. And they have a number of
13 transcripts in common and they have some unique
14 transcripts for those tissues.

15 And so the fact that you can take
16 fat-derived MSCs and you can take marrow-derived
17 MSCs and put them in a variety of assays,
18 including immunological assays, and get the same
19 readout is interpreted by me and many of my
20 colleagues to say that -- and what's missed, I
21 have to say, by many experimentalists, is that the
22 MSCs have huge sensory capabilities. They can

1 assay the microenvironment that they're in, but
2 they have a hard-wired response profile.

3 And so, therefore, if you have stroke or
4 you have heart attack and an MSC is given
5 externally and goes to those two different sites,
6 they will do the same sorts of things, but they
7 will use different molecules and different
8 molecular mechanisms. And we're only now starting
9 to understand some of those mechanisms.

10 In one study at Case Western Reserve
11 University, it's very clear that the injured
12 tissue sitting next to an MSC compared to the
13 normal injured tissues making 90 different
14 transcripts. So the therapeutic proteins in all
15 likelihood are coming from the host, not from the
16 donor. And this is I think an important point,
17 which is these cells in vivo, when they're put
18 back or they're energized in vivo, they actually
19 are sentinels for injury and assist the host in
20 regenerating tissues.

21 That's why I have strongly argued for
22 clinically homologous use. My knee joints, my

1 elbow joints, and my shoulder joints are all
2 killing me at the moment because of my age and
3 because I didn't choose my father properly. And
4 in this case the MSCs can have a very strong
5 medicinal effect. One of the clear medicinal
6 activities of MSCs is they make molecules whose
7 names we know that sit on opioid receptors. So
8 the perception of pain is decreased without taking
9 opioids.

10 And so this is another clinical aspect.
11 How can we call -- how can we justify homologous
12 use of taking fat- derived MSCs and only using
13 them in fat when -- or having fat tissue that has
14 dispersed MSCs in it as a therapeutic modality?

15 So again, I strongly oppose the concept
16 that concentrated bone marrow is an MSC product
17 because there's probably five MSCs in concentrated
18 marrow. But there's a strong, very strong,
19 paracrine activity of concentrated marrow, the
20 details of which nobody knows. But it has some
21 reported clinical outcomes.

22 And so although a hundred years ago we

1 ground up dog pancreases and gave it to diabetic
2 patients with fabulous clinical results, it's only
3 taken us a hundred years now to fabricate insulin,
4 human insulin, and deliver it to diabetic
5 patients. The cell-based therapies that are being
6 proposed and being tested clinically by
7 investigator- initiated clinical trials are
8 curative. That's not what you can say about any
9 insulin product currently on the market. And I
10 think that's an important aspect. And the aspect
11 of curative is gigantically innovative.

12 And one last sentence is that the
13 unexpected activity that MSCs make antibiotic
14 proteins, LL37, that kill bacteria on contact is
15 currently being tested with an appropriate
16 FDA-approved IND in cystic fibrosis kids who have
17 horrible lung infections. This can actually be
18 curative for those lung infections if we can get
19 this unusual antibiotic protein physiologically
20 directed at the invading bacteria. This, I think,
21 is an important completely non-homologous use of
22 these cells. However, from a paracrine standpoint

1 totally homologous.

2 DR. WITTEN: Thank you for that and for
3 that example. I think it's time to see whether
4 there are questions from the panel for some of the
5 other speakers. Thank you, Dr. Caplan.

6 Other questions?

7 DR. ANATOL: I have a question. So this
8 question is for the speaker from Wake Forest,
9 which I think might be Dr. Allickson. So in your
10 presentation you provided some examples that we
11 should consider as we move to finalize the
12 guidances. And for the homologous use guidance
13 you suggested we include an example that when
14 amniotic membrane is placed over wounds to retain
15 moisture this should be considered homologous use.
16 I'm just wondering if you see this use as
17 different than a wound covering function of
18 amniotic membrane or whether you would consider
19 them the same?

20 DR. ALLICKSON: No. What I was
21 suggesting would be simply a barrier for wound
22 healing. So I thought that that fits within the

1 361 if you look at all of it. And I thought that
2 it's an example that hasn't been demonstrated. I
3 thought it would provide clarity for people that
4 are working in that area.

5 DR. ANATOL: So as a barrier
6 specifically for wound healing?

7 DR. ALLICKSON: Yes.

8 DR. ANATOL: Okay. Thank you.

9 DR. ALLICKSON: I will submit those
10 comments. Thank you.

11 DR. WITTEN: Okay, any other questions
12 from my colleagues on the panel?

13 We're going to move on now to Session 3.
14 And we'll start -- our first speaker represents
15 the Academy of Regenerative Practices.

16 DR. COMELLA: Hi, I'm Kristin Comella
17 and I'm the president of the Academy of
18 Regenerative Practices. The Academy of
19 Regenerative Practices provides information and
20 educational programs on the clinical uses of
21 regenerative and stem cell therapies. The ARP
22 promotes regenerative medicine by teaching

1 physicians integrative and comprehensive treatment
2 methods, including bone marrow and adipose stem
3 cells and platelet rich plasma. And the ARP is
4 dedicated to providing physicians with the latest
5 regenerative clinical practices and providing the
6 data to support these therapies.

7 The role of physicians is to dedicate
8 their lives to serving the interests of the
9 patient. Market forces, societal pressures, and
10 administrative demands must not compromise this
11 principle. The role of the FDA is responsible for
12 protecting the public health by assuring the
13 safety, efficacy, and security of human and
14 veterinary drugs, biological products, medical
15 devices, our nation's food supply, cosmetics, and
16 products that emit radiation. The FDA does not
17 regulate the practice of medicine. The FDA does
18 not regulate our bodies and tissues.

19 According to the FDA's current laws, the
20 implantation of autologous HCTP's during the same
21 surgical procedure is the practice of medicine.
22 And I think that this was discussed in the last

1 session very eloquently, the concept of homologous
2 use and that the main purpose of cells is to
3 repair and maintain the tissues. So this is in
4 fact homologous use. In addition, many surgical
5 procedures are using tissues in a non-homologous
6 manner. And what we're dealing with in these
7 in-clinic stem cell procedures are surgical
8 procedures. So this is not a necessarily stem
9 cell procedure. And these therapies, such as CABG
10 with vein graft and ilium to replace the bladder
11 are in fact using tissues in a non-homologous way.

12 Also, the concept of minimal
13 manipulation was addressed earlier today, and this
14 is a process that does not alter the relevant
15 biological characteristics of cells and tissues.
16 However, many surgical procedures currently used
17 by physicians do alter the characteristics of
18 tissues. So the concept of minimal manipulation
19 does not apply to physicians in the surgical
20 procedures that may be utilized such as skin
21 grafts, hair transplants, bone grafts, and others.

22 The regenerative procedures performed in

1 clinic using the patient's own tissue do not
2 constitute a drug and, therefore, should not be
3 regulated by the FDA. Medical professionals have
4 jurisdiction over surgeries and procedures on
5 patients. Patients have a right to provide
6 informed consent on procedures involving their own
7 body and tissues.

8 I wanted to give a few examples of cases
9 that we've seen in our clinic, as well as other
10 physicians have provided me some of their slides
11 to use.

12 This is an example of a patient with
13 very thin skin, vasculitis, and as a result gets
14 these non-healing ulcer wounds repetitively. And
15 nothing was successful for this patient. When all
16 other medical therapies have failed, this is an
17 example where cell therapy using SBF and platelet
18 rich plasma was successful in healing wounds.

19 We also see very good results in
20 orthopedics. This is an example of a patient with
21 osteochondritis, and you can see the bone lesion
22 prior and then post full resolution.

1 We also have good results in
2 osteoarthritis, patients who are bone in bone with
3 limited joint space showing increased joint space
4 after an injection that was done in clinic by a
5 physician using stromovascular fraction and
6 platelet rich plasma.

7 We've done a handful of studies and
8 attempted to publish many of these studies and
9 have been successful in publishing these.
10 Unfortunately, there is a lack of funding
11 available to do these studies. So we're counting
12 on using the funds from our own, oftentimes
13 foregoing salary to perform some of these trials
14 for patients. And we've been successful in
15 studies with degenerative disc disease as well as
16 COPD. And this is an example of patients who
17 demonstrated statistically significant improvement
18 in flexion.

19 This is an example of a patient who had
20 a cancer and as a result had radiation done from
21 the nose down to the chest. And as a result, the
22 glands had been completely destroyed, so he was no

1 longer able to produce saliva. And what he told
2 us is that he was actually suicidal because he was
3 no longer able to talk, to sleep, or to eat food
4 because of the lack of saliva in his mouth. After
5 injecting the stromovascular fraction cells
6 directly into the glands, he now is producing
7 saliva and is able to live a normal life eating
8 food. Why would we deny this type of therapy to
9 this patient?

10 We've done a handful of patients for
11 traumatic brain injury. Many patients who are
12 wheelchair bound and unable to talk or walk are
13 now coming out of their wheelchairs and telling us
14 full sentences about the day that they were
15 injured. These were chronic patients two-plus
16 years post accident and now performing normal
17 activities that they never dreamed and that their
18 family never dreamed that they would perform.

19 I want to share with you two cases.
20 This is a patient with MS who was wheelchair bound
21 and her physical therapist is wiping away tears as
22 she is now walking on a walker. And her husband

1 called me to tell me he was so excited because she
2 did laundry for the first time in five years. I'm
3 not sure that's the first thing I would do.

4 This is a spinal cord injury patient who
5 was wheelchair bound two years post accident and
6 his mother said that every day he asks her to kill
7 him. She stands in the kitchen wondering if she's
8 going to have to kill her own son and would she
9 kill herself next? And now he is able to walk
10 with assistance and move his legs. He had no
11 movement from his chest down and limited use of
12 his hands.

13 These are life-changing techniques.
14 When we move these therapies forward, there are
15 going to be setbacks. There are going to be some
16 adverse events. But that can't stop the field
17 from moving forward. We have an obligation to our
18 patients and to the community to rapidly move
19 these therapies forward.

20 I want to share with you two examples.
21 In 1928, Alexander Fleming discovered antibiotics.
22 And at the time, his colleagues laughed at him.

1 He actually was giving away his antibiotics,
2 penicillin, for anyone to test in the lab because
3 he felt that it was something that was very
4 important. It wasn't until 12 years later and he
5 had actually abandoned the idea of penicillin
6 being something important that would change
7 medicine. Twelve years later there was a paper
8 published by Oxford, and at that time it became
9 very apparent that antibiotics were going to
10 change medicine. I think we have something very
11 similar on our hands right now.

12 The other example I want to share with
13 you is bone marrow transplantation. From the
14 years 1939 to 1969, there were 203 documented
15 cases. If we applied the same rules that we have
16 in place or that we're trying to put in place now,
17 this therapy would not have progressed forward
18 because 152 of the first 203 patients died.

19 These therapies are going to change
20 medicine just as bone marrow transplantation has
21 changed medicine. And it is important to note
22 that the first double-blind, placebo- controlled

1 trial for bone marrow transplantation was not done
2 until 1998, years after this had become the
3 standard of care.

4 We are the Academy of Regenerative
5 Practices and it's time to bring these therapies
6 forward to patients. Thank you.

7 DR. WITTEN: Thank you. The next
8 speaker is from the Alliance for Regenerative
9 Medicine.

10 DR. WERNER: Good afternoon, my name is
11 Michael Werner. I am the executive director of
12 the Alliance for Regenerative Medicine, also known
13 as ARM, A-R-M. We are the preeminent global
14 advocate for regenerative and advanced therapies,
15 fostering research, development, investment, and
16 commercialization of transformational treatments
17 and cures for patients worldwide. ARM is
18 comprised of about 240 life sciences companies,
19 academic research institutions, clinical centers,
20 patient advocacy groups, and investors who have
21 come together to support research and product
22 development in cell therapy, gene therapy, tissue

1 engineering, and other advanced technology
2 sectors.

3 Thank you very much for letting me speak
4 today to provide our organization's views about
5 FDA's draft guidances related to human cells,
6 tissues, and cellular and tissue- based products.
7 ARM welcomes the publication of the draft
8 guidances and commends the FDA for holding this
9 public meeting. Of course, how FDA interprets the
10 relevant provisions of the Food, Drug, and
11 Cosmetic Act and applies its regulations is
12 critically important to ensuring that safe and
13 effective products and therapies reach patients as
14 soon as possible. And we know that's a goal FDA
15 shares and indeed it's a goal I think everyone in
16 this room shares.

17 We've provided written comments in the
18 docket regarding the draft guidances, which have a
19 lot of very specific points in there and specific
20 examples of minimal manipulation and homologous
21 use and all of that. So what I'm just going to do
22 is summarize our views.

1 finalizes these guidances, it needs to take
2 actions to provide more clarity. This could take
3 several forms. Further clarification on
4 requirements for product characterization and
5 related claims for each type of product would be
6 helpful. For instance, we urge FDA to publish
7 even more examples of how the key terms such as
8 "minimal manipulation" and "homologous use" will
9 be applied to various technologies. This would
10 include when certain technologies, such as adipose
11 tissue, as we've heard a lot about today, would or
12 would not be considered more than minimally
13 manipulated and where so-called repair,
14 reconstruction, and supplementation lead to
15 findings of homologous use or not. Along with
16 these examples, we want -- we urge FDA to provide
17 detailed rationale to provide even more clarity
18 about its thinking.

19 In addition, ARM urges FDA to provide
20 flowcharts in the guidance to clearly demonstrate
21 the agency's thinking regarding evaluation of
22 these products. This would give researchers and

1 product developers a step-by-step process to
2 determine how their product will be regulated.
3 The agency could supplement its regulations and
4 guidance and include these flowcharts actually in
5 the guidance, and that would help everyone
6 understand and navigate their way through the
7 guidance and also provide the agency's assessment
8 criteria in a logical sequence. And we actually
9 provide examples of those in our written comments.

10 Finally, we think that FDA should look
11 for ways to communicate a more detailed summary of
12 the rationale for its regulatory decisions. So
13 for example, the Tissue Reference Group, the TRG,
14 processes and decisions can be made more
15 transparent. ARM urges FDA to add an appendix to
16 the draft guidance that details TRG
17 decision-making processes. It would also be
18 useful to reference where the TRG recommendations
19 are published. In general, ARM would encourage
20 FDA to allow increased interactions with sponsors
21 during the TRG process, and the agency should
22 publish a more detailed summary on the rationale

1 for each TRG classification recommendation.
2 Moreover, the website, the TRG website, should be
3 updated within one quarter of activity.

4 So I want to now turn to just a summary
5 of some specific comments on the minimal
6 manipulation and homologous use draft guidance.
7 So in terms of minimal manipulation, our comments
8 are going to address specific terminology and
9 provisions, such as we are concerned about the
10 guidances' use of the term "main function," not
11 currently a term used in regulations. If FDA is
12 going to use the term "main function," it needs to
13 be properly defined and not just in a "such as"
14 manner as it is now.

15 ARM would like to see the agency confirm
16 that the previously released list of processing
17 steps in the preamble to the 21 CFR 1271
18 regulation, which was published in 2001, remains
19 the current agency thinking. If the agency
20 thinking has changed, we request that the draft
21 guidance identify under what circumstances, if
22 any, the criteria outlined in 2001 would not

1 constitute minimal manipulation.

2 Centrifugation should be specifically
3 called out as minimal manipulation except where it
4 may affect relevant characteristics of the tissue
5 being centrifuged. This would bring FDA's
6 guidance in line with European Advanced Therapy
7 Medicinal Products Guidance, which is followed by
8 most regulatory authorities.

9 ARM believes the guidance should clarify
10 with more examples at what level a tissue
11 structure must be preserved to be considered
12 minimally manipulated. The guidance implies but
13 does not explicitly state that the primary
14 structure, including the load-bearing properties
15 of the tissue, may be changed so long as the
16 underlying tissue structure is unaffected.

17 In terms of homologous use, the guidance
18 contains a lot of precise terminology, and we
19 would recommend a glossary with definitions of key
20 terms to be used in the guidance as a way to
21 provide further clarity on how the terms should be
22 interpreted and understood. Alternatively, FDA

1 could add a reference in the guidance to the
2 definitions provided in 1271.3, which ensures that
3 these definitions reflect the agency's current
4 thinking.

5 FDA should provide additional clarity on
6 its decision to distinguish between structural and
7 nonstructural tissue and cells in its definition
8 of homologous use. We're concerned that the
9 definition provided in the document does not
10 consider the same basic function in a way
11 consistent with the guidance preamble. We
12 recommend the list of basic functions of amniotic
13 membrane be expanded to include covering and
14 protecting. And we recommend the FDA add another
15 subsection to define in more detail how homologous
16 use applies to HCTPs intended for wound healing,
17 including examples.

18 ARM appreciates FDA's efforts to
19 continually improve, clarify, and update its
20 guidance in this area, and we remain ready to work
21 with the agency on the issues in the days ahead.
22 Thank you.

1 DR. WITTEN: Thank you. Our next
2 presentation will be from the Alliance for
3 Advancement of Cellular Therapies.

4 DR. MILLER: Doctor Witten, members of
5 the panel, ladies and gentlemen, my name is Leslie
6 Miller, and I am the chairman of the Executive
7 Committee of the Alliance for the Advancement of
8 Cell Therapy, which is an organization composed of
9 patients, clinicians, and scientists involved in
10 not only the advancement of the field, but the
11 very responsible use of cell therapy.

12 I speak today as a practicing
13 cardiologist and a clinical trialist with
14 experience in over 100 clinical trials, following
15 FDA protocols and currently enrolling for trials.
16 So I have a fair perspective on this problem.

17 There is clearly a very significant
18 interest in this topic as evidenced by the
19 attendance in this meeting and the petitions to
20 speak. And I think this reflects the interest in
21 what is addressing one of the most important
22 healthcare problems in the U.S. and around the

1 world, and that is chronic disease. These
2 therapies offer potential therapy in a myriad of
3 conditions. More money is spent for the care of
4 people with chronic diseases than any other item
5 in both federal and private healthcare policies.
6 And that has to account for the greatest cause of
7 disability and loss of productivity. There are
8 estimates that range in the tens of millions of
9 people afflicted with chronic diseases, and with
10 the advancing age of this population, this is
11 going to become a more pressing problem with each
12 passing year. This cost is not sustainable and
13 new solutions need to be found.

14 We acknowledge that the FDA is facing a
15 very significant challenge in how to optimize the
16 many rapid advances taking place in many diverse
17 uses of cell therapy occurring in this field while
18 maintaining the health and safety of products. We
19 share this commitment to safety and high standards
20 for cell therapy. But research has become slow
21 and almost prohibitively expensive under the
22 current guidelines. They lead to clinical trials

1 that have often been underpowered to answer
2 critical questions on efficacy, which delays
3 progress in the field. We believe that the very
4 pressing health problem of chronic disease
5 warrants new approaches to regulation.

6 One new approach is embodied in the
7 Regrow Act, which is about to be considered by
8 Congress. This bill is not intended to alter
9 FDA's oversight role over cell therapy but provide
10 enhanced flexibility and much quicker access for
11 patients to those cells and strategies that are
12 shown to be both safe and reasonably effective in
13 well-controlled and randomized phase 2 trials with
14 increased numbers of subjects to really test the
15 therapy being evaluated and avoid the extremely
16 high cost of phase 3 trials.

17 There is ample precedent internationally
18 for adoption of accelerated pathways and
19 conditional approval for cell therapy in countries
20 like Japan and China, many countries in Europe, as
21 well as most recently Canada. We are now behind
22 these comparable countries in our response to this

1 important healthcare problem. Acceleration of the
2 approval process is feasible based on the
3 substantial record of a high degree of safety,
4 particularly autologous cell therapy, with many
5 med analyses showing as little as 2 to 4 percent
6 incidence of significant safety problems.

7 The problem in this field is that the
8 use of cell therapy has evolved rapidly from being
9 available only in FDA-approved clinical trials to
10 essentially an unregulated use in well over 500
11 clinics in this country, as well as a large number
12 outside the U.S. by practitioners with highly
13 variable training and competence. This has led to
14 many valid criticisms of this unregulated use, but
15 painted with a fairly broad brush, and has led the
16 FDA to seek an all- inclusive set of guidelines,
17 which would essentially shut down clinical access
18 to this therapy in the United States. This would
19 not only drive thousands of patients to clinics
20 outside the United States, but also disadvantage
21 the poor and those of limited resources and
22 markedly diminish the chance to gain important

1 clinical experience and trial experience with cell
2 therapy to prove its safety and efficacy.

3 We believe that there's a reasonable
4 alternative to total suppression, and that is the
5 creation of a registry of cell therapy. There is
6 ample precedent of using a well- curated registry
7 even as a control group for many phase 2 and phase
8 3 trials, including mechanical assist devices, as
9 well as their value in providing very important
10 non-protocol real world experience with a
11 treatment importantly that may show outcomes that
12 may differ from clinical trial data, both better
13 and worse. We believe that a registry could
14 address most of the valid criticisms and concerns
15 about the current unrestricted use of cell
16 therapy.

17 In order to participate, a clinic would
18 have to meet very rigorous criteria. To address
19 the concerns about incomplete data, the clinic
20 would agree to enroll every patient treated for
21 every indication and provide de- identified data
22 on the indications, symptoms, and demographics.

1 To address the variable quality of cells
2 delivered, they must obtain certification of their
3 cell preparation lab or the vendor they're using
4 and provide complete data on source preparation
5 type, number, quality, route, et cetera, of the
6 cells delivered. To assure the valid treatment
7 strategies, they would use IRB approved protocols
8 for every indication based on published data.

9 To address the major concern that
10 patients get variable and potentially inflated
11 expectations of this therapy, we propose the use
12 of a novel scripted narrative that can be reviewed
13 and approved by the FDA, which would then be
14 videotaped and provided to each patient to assure
15 a fair and balanced information provided to their
16 families as well to allow adequate time for
17 questioning before they commit and consent to
18 these procedures. And it would include consent to
19 provide required follow up.

20 To address the lack of reliable
21 meaningful data there'll be the use of only
22 endpoints and metrics utilized in published

1 clinical trials. The mandated follow-up would
2 occur with trained objective observers to document
3 both good and adverse outcomes. To assure the
4 reliability of the data without internal conflict,
5 they would use an independent company to control
6 all data and assure compliance. The patients and
7 the clinics would submit all data within one month
8 of the uniform time or be potentially suspended
9 for a period until that data is up to speed.

10 One of the most important aspects of the
11 data in the registry is complete transparency and
12 the ability to audit every aspect of the data,
13 including outcomes, by the FDA. But also for
14 patients who are seeking treatment to assure the
15 highest quality centers and treatments with real
16 time available to make the most informed decision.

17 We have no doubt that this
18 recommendation would reduce the number of clinics
19 providing cell therapy to a relatively small
20 number initially. But we believe that this could
21 provide the FDA with a much needed high quality
22 data on safety and efficacy of cell therapy and

1 allow continued access for patients of those
2 clinics that are willing to meet these very high
3 standards with enhanced confidence of very high
4 quality care.

5 I hope the FDA will consider this
6 proposal. Thank you.

7 DR. WITTEN: Thank you. Our last
8 speaker before the break is from the Alliance of
9 Wound Care Stakeholders.

10 DR. KIM: My name is Paul Kim. I'm
11 pleased to be here today representing the Alliance
12 of Wound Care Stakeholders. The Alliance is a
13 nonprofit multidisciplinary trade association of
14 physician medical specialties, societies, and
15 clinical associations whose mission is to promote
16 quality care and access to products and services
17 for people with wounds through effective advocacy
18 and educational outreach in the regulatory
19 legislative and public arenas. Several of the
20 professional organizations to which I belong are
21 members of the Alliance. Most of the Alliance
22 clinical members use tissue products in their

1 practices and thus have a vested interest in
2 ensuring patient access to these important
3 products, which may be jeopardized based on the
4 language contained in the guidance documents.

5 By the way of background, I've been
6 working in wound care and limb salvage for the
7 past 11 years. I'm an associate professor in the
8 Department of Plastic Surgery and the director of
9 research through the Division of Wound Healing and
10 Hyperbaric Medicine at Georgetown University
11 Hospital. While I'm speaking on behalf of the
12 Alliance, many of my comments are based on my own
13 personal clinical experiences both in research as
14 well as in treating patients with wounds with the
15 types of products that are the subject of this
16 hearing.

17 My comments today will focus on two of
18 the four guidance documents, minimal manipulation
19 and homologous use. These two concepts are so
20 interrelated that while it is appropriate to have
21 separate guidance documents for each, there must
22 be consistency between the two documents.

1 Furthermore, while each of the guidance documents
2 should provide specific detail or to give greater
3 clarity and guidance, this does not occur in these
4 particular documents. In fact, many examples that
5 were previously provided have been eliminated.
6 More importantly, there are too many significant
7 new requirements within the minimal manipulation
8 document which not only conflict with homologous
9 use document but conflict with the current
10 regulatory language.

11 There are two main areas of concern for
12 the Alliance in the minimal manipulation document.
13 Number one, the term "main function" introduced in
14 this document conflicts with the current
15 definition of "homologous use." Number two, the
16 change regarding how minimal manipulation is
17 determined that specifically focus on the main
18 function of the tissue in the donor rather than
19 what is written in current law by the function of
20 the tissue in the recipient.

21 First I'd like to address the newly
22 created term "main function" in the minimal

1 manipulation guidance document. The notion that
2 these tissues have a main function which
3 determines whether a product is structural or
4 nonstructural conflicts with the current
5 regulation, as well as the draft guidance document
6 on homologous use. The conflict with homologous
7 use guidance is problematic. It is not possible
8 to separate homologous use from minimal
9 manipulation. When considering whether or not a
10 product is regulated as a 361 ACTP, the homologous
11 use guidance document accurately utilizes the term
12 "basic function/functions." And we recommend that
13 the FDA continue to utilize the term "basic
14 function and/or functions."

15 Furthermore, it is misleading and
16 clinically inaccurate to state that the tissue has
17 a main function. Tissue products have more than
18 one function, and to restrict their use to one
19 function, the main function, is scientifically and
20 clinically incorrect. Tissues even without cells
21 may have more structural impact upon application
22 or implantation.

1 For example, amnion contains not only
2 collagen in an extracellular matrix, it has other
3 proteins and other biologic that provide other
4 biologic functions. Minimal manipulation of ECM
5 and processing should maintain the ECM biochemical
6 factors such as fibronectin, gags, PGs, and
7 laminates that are local biological effects like
8 the organization of cell migration and
9 facilitation and cell attachment that are beyond
10 providing a simple structural support. Cell
11 attachment elicits another cascade of activity
12 related to restoration of healing processes that
13 were absent prior to placement of the donated ECM.
14 We can't achieve this with synthetic dressings.

15 Many HCTPs have more than one function
16 which should be included in these guidance
17 documents. For example, there are different
18 tissue types that we should be -- would be subject
19 to this guidance, and all should be broken into
20 specific areas, including but not limited to
21 dermis, epidermis, amniotic, chorion. Each of
22 these tissue types have multiple functions and not

1 simply a main function. For example, basic
2 functions of placental tissue or amniotic
3 membranes can include preventing infection, rapid
4 self-restoration, allowing free movement, a
5 protective barrier, and a cover. With or without
6 maintenance of the donor cells, many of these
7 basic functions are sustained and observed after
8 placement in the recipient. By utilizing most of
9 the basic function or functions within the
10 definition of placental tissue, a clinician can
11 apply placenta-derived tissues as part of good
12 wound care, treatment for a variety of wound types
13 and severity.

14 If the notion of main function was
15 adopted, then dermis-derived allografts would not
16 be used to treat wound care patients. Yet there
17 are several studies published providing evidence
18 of the clinical benefit of the dermis- only
19 allografts when used in treatment regimen of full
20 thickness chronic wounds.

21 The Alliance urges the FDA to eliminate
22 the term "main function" and instead utilize the

1 term "basic function or functions of tissue."

2 With respect to the second issue, the
3 FDA changes how minimal manipulation is
4 determined. Under current law, whether an HCTP is
5 considered to be more than minimally manipulated
6 is determined by the tissue's function in the
7 recipient. Thus, for structural tissue, the
8 analysis -- excuse me, the Alliance is concerned
9 with the effects that processing has on the
10 tissue's utility for reconstruction, repair or
11 replacement. The draft guidance, however,
12 analyzes minimal manipulation, reports minimal
13 manipulation in terms of main function of the
14 HCTP. It focuses on the main function of the HCTP
15 in the donor.

16 We are extremely concerned about this
17 departure. Tissue adapts to its environment.
18 Tissue is often explanted from one area and
19 successfully used in different areas of the body.
20 Just because a tissue may come from a uterus does
21 not mean it must be transplanted into a uterus.
22 Any tissue used must function in the recipient in

1 the manner required by that of the recipient,
2 regardless of the product origin or the source of
3 the material. The extracellular matrix of tissues
4 are basically the same regardless of where it is
5 placed. The microenvironment into which donated
6 tissue is placed guides its remodeling, its
7 functionality.

8 Historically, several sources of tissue
9 have been used in wound care with success:
10 peritoneum, fascia, pericardia, skin, placental
11 membranes, and blood components. The Alliance
12 recommends that the analysis should be based on
13 the effects of the -- that the processing has in
14 the tissue's utility for reconstruction, repair,
15 or replacement in the recipient. It's not only
16 more accurate, it is also what is currently
17 required in the regulations.

18 The Alliance does have two specific
19 issues regarding the homologous use guidance
20 document. First, the Alliance is concerned about
21 how narrow the definition of homologous use for
22 amnion tissue will impact its use for wound care.

1 There are many functions of amniotic tissue, as we
2 described earlier. And this tissue type should be
3 used for wound healing. The FDA has even stated
4 in the past that amnion may be used for wound
5 healing when cytokines were present. Meaning that
6 it was not decellularized. As such, the Alliance
7 recommends that the FDA continue to permit amnion
8 in their homologous use consideration.

9 Finally, the Alliance would like to
10 state that regulations expressly do not separate
11 the definition "homologous use" depending on
12 whether tissue is structural or nonstructural.
13 And that's been raised before in this session.

14 On behalf of the Alliance, I thank you
15 for the opportunity to provide you with our
16 testimony. We'll be submitting written comments
17 later this month.

18 DR. WITTEN: Thank you. We're going to
19 take a break now. We're running a little bit
20 early so that we'll reconvene at 3:15. So can
21 everyone be back in their seats at 3:15.

22 (Recess)

1 DR. WITTEN: Our first speaker during
2 this session will be from the American Association
3 of Blood Banks.

4 DR. KAMANI: Good afternoon. My name is
5 Naynest Kamani. I'm the vice president for
6 cellular therapies and research at AABB, formerly
7 known as the American Association of Blood Banks.
8 AABB is an international not-for-profit
9 professional association representing
10 approximately 7,500 individuals and about 1,500
11 institutions involved in the fields of transfusion
12 medicine and cellular therapies. AABB advances
13 the practice and standards of transfusion medicine
14 and cellular therapies to optimize patient and
15 donor care and safety. AABB appreciates the
16 opportunity to provide comments on the draft
17 guidance documents relating to the regulation of
18 human cells, tissues, and/or cellular or
19 tissue-based products. Additionally, AABB
20 applauds the FDA for its efforts to thoughtfully
21 regulate the HCTP industry in order to maintain
22 patient access to safe and effective cellular

1 therapies.

2 We have comments pertaining to three out
3 of the four draft guidance documents that are the
4 subject of today's public hearing. First one is
5 on the minimal manipulation of human cells,
6 tissues, and cellular and tissue-based products.
7 AABB requests clarification on two sections of
8 this document. First one, the working definition
9 of "minimal manipulation" and the second on the
10 specific examples of nonstructural and structural
11 tissue.

12 With respect to minimal manipulation, we
13 request further clarification on whether forms of
14 processing such as cutting, grinding, or enzymatic
15 digestion of tissues such as cord tissues prior to
16 cryopreservation for potential future isolation of
17 cells such as mesenchymal stromal cells would meet
18 the definition of minimal manipulation.

19 Secondly, in the same guidance document,
20 the FDA has provided a limited list of examples
21 that the agency considers as either structural
22 tissues or as cells or nonstructural tissues.

1 AABB requests that these lists be expanded to
2 include other tissues that are currently collected
3 from donors and either stored or manipulated for
4 subsequent use. We request clarification on
5 whether tissues such as cord tissue are considered
6 as structural tissues. Included on the list of
7 examples for cells or nonstructural tissues are
8 lymph nodes and parathyroid glands. We request
9 further clarification on what other tissues, for
10 example, tissues such as thymic tissue or the
11 thymus gland, whether they would qualify as
12 nonstructural tissues as well.

13 Our second set of comments is on the
14 same surgical procedure exemption under 21 CFR
15 1271, questions and answers regarding the scope of
16 the exception homologous use of HCTPs. AABB
17 requests clarification on the requirements for
18 intraestablishment transfer of HCTPs. The
19 guidance states that the same surgical procedure
20 exception applies when HCTPs are for autologous
21 use implanted in the same surgical procedure and
22 remain in their original form with maintenance of

1 safety and sterility. Temporary storage for a few
2 days between the time of collection and use would
3 qualify for SSP exception, as long as the HCTP is
4 not manipulated other than rinsing, cleansing,
5 sizing, and labeling, and the administration and
6 collection are occurring at the same
7 establishment. We need clarification as to
8 whether the SSP exception is applicable if the
9 stored HCTPs are being transported from one
10 building or facility to another building or
11 facility within the same establishment.

12 Our third set of comments is on the
13 guidance regarding homologous use of HCTPs. AABB
14 requests further clarification from the agency on
15 the guidance for the homologous use of HCTPs for
16 the following circumstances. First, we request
17 the inclusion of examples in this guidance that
18 address the use of whole blood marrow aspirates or
19 enriched concentrates of bone marrow-derived stem
20 cells or blood or bone marrow-derived platelet
21 rich plasma, or PRP. We also request
22 clarification on whether the effects of

1 platelet-derived growth factors in PRP are
2 considered as having systemic effects. Because
3 this would then have implications for whether it
4 would be characterized as homologous use or
5 minimal manipulation.

6 We appreciate this opportunity to
7 provide these comments and will be submitting
8 these in an electronic format within the next
9 couple of weeks. Thank you.

10 DR. WITTEN: Thank you. Our next
11 speaker represents the American Association of
12 Tissue Banks.

13 DR. WILTON: Thank you. My name is
14 Frank Wilton, and I'm the president and chief
15 executive officer of the American Association of
16 Tissue Banks, or AATB. In my allotted time, I
17 would like to provide a brief background on human
18 tissue and its safety, highlight some positive
19 aspects of the guidance documents, and then
20 summarize our key recommendations for improvement.

21 Before I delve into the specifics of the
22 guidance documents, I want to first touch upon the

1 issue of safety. Like FDA, the AATB diligently
2 monitors and audits tissue safety. If a safety
3 issue is identified, the AATB quickly establishes
4 new standards to further reduce the risk of
5 potential harm. Due to that strong diligence,
6 human cells, tissues, and cellular-based tissue
7 products, or HCTPs, have a stellar safety record
8 as outlined on this slide. Given that excellent
9 safety record, I must admit that we at the AATB
10 were a bit taken back by some of the FDA's current
11 thinking with respect to the regulation of HCTPs
12 as it is described in the guidance documents. We
13 have worked to diligently respond to the request
14 for comment and provide additional science
15 background information related to the application
16 to particular HCTPs and of course recommendations.

17 As we seek to improve the guidance
18 documents, we must stay grounded in the supporting
19 science and regulations. This slide contains two
20 key aspects of the regulations. The first denotes
21 the agency's presumption related to the
22 application of the term "homologous use" and the

1 second highlights the opposing but supportive
2 goals of maintaining safety and access or
3 availability. So I will discuss in a few minutes
4 our recommendations for improvements focused
5 primarily on ensuring that the guidance documents
6 more closely adhere to these underlying regulatory
7 tenets.

8 Harkening back to the balance between
9 access and safety, I provide this slide to simply
10 highlight that, per our review of the guidance
11 documents and further detailed in our comments,
12 our primary concern is that more than a quarter of
13 a million patients will be potentially denied
14 access to currently marketed HCTPs. Given the
15 safety record, it is unclear why the agency feels
16 as if the access to current therapies should be
17 dramatically affected.

18 As you probably ascertained from our
19 previous comment letters, one key issue is the
20 newly introduced concept of "main function."
21 Procedurally, this is such a departure from
22 current regulation that we feel it is not

1 appropriate for a guidance document but better
2 suited for notice, comment, and rulemaking. The
3 procedural shortcomings become even more important
4 in light of our serious substantive concerns with
5 this new term. Rather than focus on a
6 predetermined function for a tissue category, such
7 as all adipose, we believe the agency should
8 retain its current review of HCTPs on a
9 case-by-case basis. In that manner, it is the
10 basic function or functions highlighted by the
11 manufacturer's objective intent which determines
12 whether a specific product is structural and/or
13 nonstructural in applying the definition of
14 minimal manipulation.

15 Under the previous regulations, the
16 agency provided a list of processing steps that
17 were generally determined to be within the rubric
18 of minimal manipulation. However, in crafting
19 these guidance documents, the FDA has omitted that
20 list. We believe it should be restated and
21 expanded. We understand the limitations of that
22 list, that it applies generally and not

1 specifically. However, especially in light of
2 numerous new guidance documents, providing some
3 general clarity would be exceptionally helpful.

4 Before I delve into my next
5 recommendation, I'd like to highlight how the
6 agency described the process for determining
7 whether a product was minimally manipulated within
8 the 2006 Jurisdictional Update, or JU. As this
9 slide highlights, the determination was made on a
10 case-by-case basis, weighing the potential
11 effects, both positive and negative.
12 Unfortunately, the agency has moved away from that
13 construct in these draft guidance documents and
14 seems to be putting the onus on tissue banks and
15 others to prove that a product is a 361 HCTP
16 rather than weighing it on a case-by-case basis.
17 We respectfully recommend that the agency revert
18 to its previous position related to minimal
19 manipulation and the eligibility presumption.

20 While I do have some comments on the
21 homologous use guidance as denoted on this slide,
22 I want to note that AATB was generally less

1 concerned with the latter developed draft guidance
2 documents because, other than what is noted here,
3 the homologous use draft guidance document
4 primarily hues closely to the regulations and
5 FDA's previous interpretations. And, most
6 significantly, this draft guidance did not contain
7 the new and poorly defined term "main function."

8 That said, I want to end my time in
9 front of you on a positive note. Not only has the
10 FDA provided a formal comment period, which did
11 not occur with the 2006 Jurisdictional Update, but
12 you've opted to have this hearing. In addition,
13 recognizing that all these draft guidance
14 documents are interrelated, you extended the
15 formal comment period. Finally, we are pleased to
16 note that you reflected upon our comments from the
17 2006 JU and included our suggested definitions of
18 the terms "original" and "relevant." I'm hopeful
19 that upon reading the final guidance documents the
20 AATB will be able to note more situations where we
21 feel as if our recommendations were truly heard
22 and acted upon.

1 Finally, I would like to highlight that
2 AATB understands just how difficult it is to
3 develop key guidance documents. As the FDA is
4 aware, the AATB shared its particular guidance
5 document recommendation related to homologous use
6 with FDA just before the FDA released its own
7 document.

8 Further, since that time, the AATB, and
9 in particular the Tissue Policy Group, or TPG, has
10 focused on a much more comprehensive guidance
11 document. This guidance document, which we will
12 submit to the docket prior to the close of the
13 comment period, expands upon the homologous use
14 draft guidance document recommendation by adding
15 new discrete concepts. Namely, as the title
16 suggests, the main features of this guidance
17 document recommendation is to provide a framework
18 for the appropriate analysis, characterization,
19 and assessment of HCTPs based on the
20 manufacturer's objective intent. This document
21 further details key linkages between core
22 regulatory concepts growing on clear regulatory

1 link between the manufacturer's objective intent,
2 the homologous use, the original relevant
3 characteristics, and the appropriate methodologies
4 for analysis, characterization, and assessment.
5 Finally, it also contains HCTP flow diagrams,
6 given the need for additional clarity in this
7 area. The vast majority of tissue utilized within
8 the United States follows this guidance already.

9 Thus, we hope the FDA will review this
10 document in its entirety before finalizing the
11 guidance documents. If we were not so pressed for
12 time, I would spend much more time talking about
13 this document given its importance. We encourage
14 the FDA to hold a workshop on the topic and we
15 would be happy to collaborate with FDA on it.
16 Thank you for your time.

17 DR. WITTEN: Thank you. Our next
18 speaker represents the American College of
19 Surgeons.

20 DR. GLASBERG: Good afternoon. As a
21 governor with the American College of Surgeons,
22 I'd like to thank the FDA for convening this Part

1 15 hearing. My name is Dr. Scott Glasberg, and
2 I'm pleased to be able to present to you this
3 afternoon regarding fat grafting and its
4 application crossover in a variety of surgical
5 specialties.

6 First, I'd like to take the opportunity
7 to provide you with some background on the
8 American College of Surgeons. Founded in 1913,
9 the American College of Surgeons was the premier
10 scientific and educational organization for
11 surgeons numbering more than 80,000. The American
12 College of Surgeons is a global organization with
13 more than 6,600 fellows in other countries, making
14 it the largest organization of surgeons in the
15 world.

16 As this slide highlights, the fat
17 grafting procedure has three major components.
18 Fat harvesting, in which the patient is
19 anesthetized and the fat is usually removed by a
20 stent or liposuction technique. Once harvesting,
21 minimal processing is used to clean the fat and
22 separate it from the lipoaspirate using methods

1 such as centrifugation, washing, and filtering.
2 Then the fat is transferred and implanted into the
3 desired location. To put it in simpler terms, fat
4 grafting involves harvesting with liposuction or
5 tumescence, simple processing, which may include
6 centrifugation, washing, and filtering, and
7 implantation of the graft with a syringe and blunt
8 cannula. Most importantly this slide highlights
9 activities that are not considered related to fat
10 grafting by the American College of Surgeons and
11 the American Society of Plastic Surgeons, namely
12 concentrating stem cells, advertising related to
13 the stem cells, or the addition of any types of
14 additives, such as P188.

15 It is our understanding the agency is
16 looking to produce a document that will allow
17 surgeons to reflect and determine what is the
18 standard and appropriate use of adipose cellular
19 transplantation. So it's for this reason we've
20 included these procedures which we felt fall
21 outside the realm of current standards of fat
22 grafting.

1 While most of you are familiar with fat
2 grafting within plastic surgery, I want to
3 highlight that fat grafting is used in many
4 surgical specialties to help a variety of
5 procedures, such as the reversal and modulation of
6 scarring, modulating pain, including pain related
7 to amputation sites, reversal of damage done by
8 therapeutic radiation, the treatment of bed sores,
9 medical care for vocal cord paralysis, therapy for
10 velopharyngeal insufficiency, medical care for
11 scleroderma and other systemic sclerosis,
12 treatment for Dupuytren's Contracture and
13 Reynaud's phenomenon, and additionally into joints
14 in orthopedic surgery.

15 Of course, given that there's a wide
16 application for numerous surgical related issues,
17 it's important to ensure that within the practice
18 of medicine there is appropriate informed consent.
19 This slide highlights some of the key components
20 of that consent process, especially as it relates
21 to the long-term effects of fat grafting as well
22 as combining it with other procedures. And

1 appropriate consultation involves a description
2 not only of the procedure but the associated risk
3 and safety issues for that procedure as well. Fat
4 grafting is considered safe to be performed with
5 other surgical procedures such as breast
6 augmentation, revisional breast surgery, and
7 breast reconstruction. There are many other
8 surgical procedures where fat grafts may be
9 included, including facelifts, abdominoplasty,
10 liposuction, the treatment of open wounds, and
11 others that I've mentioned earlier.

12 In reviewing the draft guidance
13 documents, I'd like to highlight some key
14 concerns. With respect to the adipose draft
15 guidance, we would like the FDA to expand the
16 categorization of adipose tissue from exclusively
17 structural to both structural and nonstructural,
18 depending on its intended use. In addition, we
19 would like the FDA to revise their position that
20 decellurizing the adipose tissue necessarily
21 diminishes its ability to perform its structural
22 function.

1 With respect to the same surgical draft
2 guidance document, we would appreciate it if the
3 FDA would clarify that centrifugation of
4 liposuction aspirates in preparation for
5 autologous fat grafting falls within the same
6 surgical exception.

7 The next few slides highlight specific
8 language changes that the American College of
9 Surgeons believe will address these concerns. Our
10 understanding is that the FDA has requested
11 specific changes to the draft and that's why we're
12 providing them here.

13 With regards to adipose, we request that
14 the FDA revise the guidance to recognize adipose
15 can have both structural and nonstructural
16 functions. We also request that the FDA examine
17 the individual HCTP and the manufacturer's
18 objective intent to determine whether it is
19 structural or nonstructural rather than focusing
20 on the tissue character category, for example
21 adipose tissue.

22 In addition, we believe that

1 decellularization and delipidation in and of
2 itself should not be more than minimal
3 manipulation. FDA guidance noted that adipose can
4 have connective properties similar to dermis. As
5 such, decellularization of adipose similar to
6 dermis should not result in more than minimal
7 manipulation. Examples noted below.

8 With regards to the same surgical
9 guidance document, we believe that a new FAQ
10 should be added in the guidance to clarify which
11 -- what certain manufacturing steps beyond
12 rinsing, cleansing or sizing are generally
13 included within the exception, including
14 centrifugation of liposuction aspirates in
15 preparation for autologous fat grafting.

16 Before I actually say thank you, given
17 some of the comments I heard this morning with
18 regards to registries, I wanted to make one
19 comment with regard to that. You'll be hearing
20 some comments later today and tomorrow from the
21 American Society of Plastic Surgeons and the
22 Plastic Surgery Foundation regarding the graft

1 registry, which is a registry which was initiated
2 this year and is now currently up and running
3 among member surgeons. That is currently gaining
4 a significant amount of impetus and data within it
5 as mentioned. As would be desired, it's a
6 real-time registry with real-time data giving
7 real-time analysis of that data. So I would
8 appreciate if the FDA would consider that registry
9 in its deliberations.

10 Again, many thanks for providing me the
11 opportunity to speak today. I hope that I have
12 been able to educate you slightly on fat grafting
13 across various surgical specialties, as well as
14 provide some key recommendations to ensure that
15 our patients have continued access to these key
16 procedures. The American College of Surgeons is
17 committed to ensuring patient safety while still
18 providing the most innovative surgical techniques
19 for our patients. And I'll welcome any questions
20 that you have later on. Thank you very much.

21 DR. WITTEN: Thank you. Our next
22 speaker is from the American Society of Plastic

1 Surgeons.

2 DR. RUBIN: Good afternoon. First I'd
3 like to thank the FDA for hosting this Part 15
4 hearing. My name is Dr. Peter Rubin, and I'm here
5 on behalf of the American Society of Plastic
6 Surgeons to further discuss issues relevant to
7 board certified plastic and reconstructive
8 surgeons and our patients.

9 Before I begin, I would like to provide
10 a little more background on the ASPS and our work.
11 As this slide indicates, the Society represents
12 nearly all board certified plastic surgeons
13 practicing in the United States.

14 One key issue raised by the draft
15 guidances is the appropriate regulation of
16 autologous fat grafting. Therefore, the focus of
17 my presentation will be to provide more background
18 on such procedures, including its long history, as
19 well as provide specific recommendations to the
20 draft guidances to address any concerns
21 board-certified plastic surgeons may have with
22 respect to fat grafting. As this slide indicates,

1 fat grafting is a form of tissue grafting in which
2 fat is acquired from the patient using a simple
3 hollow bore cannula placed into the subcutaneous
4 tissues to which suction, vacuum suction, is
5 applied. The tissue is then gently centrifuged to
6 separate the layers, a very minimal processing
7 step, before being reinjected into the same
8 patient.

9 Given the simplicity of the procedure it
10 should not be surprising to note that fat grafting
11 has actually been around for over 100 years, from
12 Gustav Neuber first transplanting fat in 1893 to
13 recognition of the regenerative potential and the
14 development of injectable methods. And the
15 ultimate expansion of application to numerous
16 reconstructive applications throughout the body,
17 including military applications.

18 As this slide demonstrates, fat grafting
19 is really integral to the practice of plastic
20 surgery for a variety of clinical purposes and not
21 surprisingly has been widely integrated into
22 routine plastic surgery practice with many

1 thousands of cases being done across the nation
2 every year, and especially as it relates to breast
3 cancer reconstruction. Seventy percent of U.S.
4 plastic surgeons have used fat grafting techniques
5 for breast operations, and

6 percent of those plastic surgeons said
7 that they use fat grafting for reconstruction
8 techniques and often apply fat grafting along with
9 implants or flap procedures. Fat grafting is a
10 key option for treating other post mastectomy
11 conditions, including reversing damage caused by
12 therapeutic radiation, the remodeling effects, and
13 reducing breast implant-related breast pain and
14 post-mastectomy pain.

15 I'd like to take a minute or so to
16 explain the relevance to breast reconstruction.
17 As we all know, breast reconstruction aids in
18 restoring the whole person after a woman has
19 undergone surgery to remove breast cancer.
20 Several federal laws have helped preserve and
21 protect a woman's ability to have breast
22 reconstruction surgery and critical to many of

1 those surgeries is the ability to use fat
2 grafting. With that in mind, you can imagine our
3 concern with this particular example within the
4 draft adipose guidance suggesting that fat
5 grafting to the breast, such a widely practiced
6 procedure with great benefits to our patients, is
7 considered non-homologous use. As we see in the
8 guidance document, in Example B3, this states that
9 adipose tissue is recovered and processed for
10 injection to the breast as reflected by the
11 labeling, advertising, or other indications of the
12 manufacturer's objective intent for non-implant
13 based augmentation.

14 The breast is composed of lobes of
15 glandular tissue and branching ducts interspersed
16 with fat and ligaments that support the breast and
17 give it shape and nerves, blood vessels, and
18 lymphatic tissues. The basic function of the
19 breast tissue is to produce milk, lactation, after
20 childbirth. Because this is not a basic function
21 of adipose tissue, using HCTPs from adipose
22 tissues for breast augmentation would generally be

1 considered a non-homologous use.

2 Now this language is actually very
3 problematic and has unintended consequences. As
4 this slide highlights, fat grafting to the breast
5 is most certainly a homologous use. Adipose
6 tissue, which is naturally present in breast
7 tissue, is a structural component. As a
8 structural component is injected to the breast to
9 preserve the structure and function of the
10 secondary sex organ, and as such should be
11 considered homologous use. Moreover, lactation is
12 not the sole function of the breast. Lactation is
13 only a function of the breast during the very
14 limited period following childbirth. In contrast,
15 throughout a woman's adolescence and adulthood,
16 the breast's main function is that of a secondary
17 sex organ.

18 To further highlight this point, I'd
19 like to show this illustration which clearly
20 depicts the presence of fat tissue in the breast
21 as a normal structural component throughout the
22 breast. The basic function of adipose tissues

1 includes providing structural support to define
2 the shape of the human body. Autologous adipose
3 is used to supplement, repair, and replace the
4 breast tissue during breast augmentation or
5 reconstruction. Therefore, this is a homologous
6 use of adipose.

7 I'd like to further emphasize that no
8 method of breast reconstruction restores
9 lactation. Implant-based reconstruction restores
10 form but not lactation. Fat-based breast
11 reconstruction has been around for decades and
12 also does not restore lactation. A very
13 significant unintended consequence of this draft
14 guidance is that it will eliminate the gold
15 standard for breast reconstruction surgery, the
16 free flap procedure. As we see in this diagram,
17 the free flap procedure is a process by which a
18 mass of adipose tissue is removed completely and
19 then reconnected by microsurgery. So completely
20 removed and transferred to another part of the
21 body or reimplanted by microsurgery. Without a
22 change to the draft guidance document, the gold

1 standard procedure would not be allowed.

2 Given these concerns, we respectfully
3 suggest a modification of the language to ensure
4 that women have access to all options for breast
5 reconstruction. The suggested language that we
6 propose is that we suggest that you modify Example
7 B3 so that it reads, "Adipose tissue is recovered
8 and processed for injection into the breast as
9 reflected by labeling, advertising, or other
10 indications per the manufacturer's objective
11 intent for nonimplant breast augmentation."
12 Because adipose is already within the breast to
13 provide structural support and shape, using HCTPs
14 from adipose tissues for breast augmentation or
15 reconstruction would generally be considered a
16 homologous use.

17 The language should not distinguish
18 between breast augmentation and breast
19 reconstruction. And the basic language should
20 acknowledge that the breast has multiple functions
21 and not rely on the basic function.

22 Once again I express my thanks to the

1 FDA for the opportunity to present on behalf of
2 the American Society of Plastic Surgeons and our
3 patients. Thank you.

4 DR. WITTEN: Thank you. Our next
5 speaker is from the Biologic Orthopedic Society.

6 DR. MISHRA: Good afternoon. I'd like
7 to thank the FDA panel members for organizing this
8 important meeting. I'd like to thank the NIH for
9 hosting us here in beautiful Bethesda. And I'd
10 like to introduce myself. My name is Dr. Allan
11 Mishra, and I represent the Biologic Orthopedic
12 Society.

13 I'm going to start today with why. Why
14 am I here? I'm here because we need better
15 treatments for our patients. The status quo is
16 simply not any longer acceptable. And if we're
17 going to change the status quo, we need to look
18 for better solutions. And my suggestion for the
19 panel, for the participants, and for the people
20 who are watching online is that it's possible that
21 the power to heal can come from within.

22 Now, the Biologic Orthopedic Society is

1 a group I started about four or five years ago and
2 I thought there'd be 50 to 100 like-minded
3 individuals. We are now over 5,800 professionals
4 dedicated to advancing the research and
5 development of biologic treatments for
6 musculoskeletal disorders.

7 And what we've found and what I would --
8 almost all of us know this already intuitively,
9 our bodies have amazing healing power. I'm going
10 to give you three specific examples.

11 Who in here has cut themselves either
12 shaving or a paper cut in the last week? Okay, so
13 next time you do that, what happens? You bleed.
14 And what do you do? Maybe you push on it, you put
15 a little Band-Aid on it, and it gets better within
16 a week.

17 As an orthopedic surgeon, most
18 fractures, simple fractures, will heal with
19 immobilization and a little bit of time. And
20 what's interesting is your liver has the most
21 robust proliferative capacity or generative
22 capacity. If you could actually take out a lobe

1 of your liver, transplant it to somebody else,
2 then that lobe of your liver will regenerate. So
3 skin, bone, and liver are three specific examples
4 of our body's ability to heal itself.

5 Now, other tissues need a little bit of
6 a helping hand. Skin, bone, and liver don't
7 always heal, but other tissues sometimes need more
8 of a helping hand. And where can we get that?
9 Well, what if the solution -- I mean, we're
10 spending billions and billions of dollars on
11 healthcare, but what if the solution to
12 challenging healthcare problems actually existed
13 within our own bodies? We've heard some amazing
14 talks today already about how that's possible.
15 And I'm going to suggest to you that it may be.

16 What are the areas that we can look at?
17 The simplest three are blood, bone marrow, and
18 adipose tissue. I'm very happy because we had to
19 turn in our slides about six weeks ago. I had to
20 pick one of these three to focus on, and for the
21 next four or five minutes I'm going to focus on
22 blood.

1 double-blind prospective randomized trial using
2 PRP for chronic tennis elbow. And what we found
3 is there are no significant adverse effects. And
4 that's actually kind of pretty obvious. If you're
5 using a component of your own blood and injecting
6 it back into your own arm, it should be okay.

7 Surprisingly, we actually found an
8 interesting signal of efficacy in that study. At
9 24 weeks, there were significantly more patients
10 who were successfully treated compared to the
11 control. And what should be embarrassing to the
12 Americans in this room is that this data along
13 with other data has allowed this to be approved in
14 Europe and in Japan, but not technically in the
15 United States. So the data that we generated here
16 is being used overseas. And this isn't just my
17 opinion. Published in The American Journal of
18 Sports Medicine, the leading sports medicine
19 journal in the world, this June was a meta
20 analysis of randomized clinical trials concluding
21 that PRP is of great clinical significance.

22 So if you think about it, blood is safe,

1 a component of blood can be used effectively, and
2 blood is not a drug. A drug is a chemical or
3 plant-derived substance that can be intended for a
4 physiologic system. Blood is really a naturally
5 derived product.

6 And I think this is my most important
7 slide. Patients should be allowed to use
8 components of their own body to help heal
9 themselves. Let me maybe waste my time a little
10 bit and say patients should be allowed to use
11 components of their own bodies to help heal
12 themselves. I think that's one of the most
13 important things we can think about moving
14 forward.

15 In the last two to three minutes I'll
16 talk about how blood is connective tissue and how
17 it should be used for homologous use. Connective
18 tissue is supporting tissue that surrounds other
19 structures. Blood, according to Pub Med Health,
20 is included in that connective tissue list. So
21 connective tissue is derived from embryonic
22 mesoderm like other connective tissues and

1 consists of a matrix of cells designed to support
2 other tissues.

3 So if you take those two and you put
4 them together and you say, is blood connective
5 tissue? And if you're going to use it to treat
6 other types of connective tissue, it should be
7 considered homologous use. And I can go into much
8 more detail in comments that I'll submit.

9 The final thing that I'd like to talk
10 about for two minutes, is we need to move at the
11 speed of war. And I have to -- I can't take
12 credit for this, this comes from a new friend of
13 mine. He is Captain Tom Chaby. He is a former
14 commanding officer of U.S. Navy SEAL Team 5, and
15 he now is running the Warrior to Warrior
16 Foundation, which is trying to help our veterans
17 as they return from war with musculoskeletal
18 issues and other significant problems. He really
19 believes in two things: fast action and rapid
20 reaction. And it's not just our vets that are
21 facing incredible musculoskeletal problems, it's
22 all of us. Almost everybody in this room probably

1 has something wrong with them from their
2 musculoskeletal standpoint. So over 125 million
3 Americans, \$200 billion annually, 16 percent of
4 all of our healthcare costs. And what's happening
5 is an explosion of utilization. You're not going
6 to die from the arthritis, probably not going to
7 die from a disc herniation, but we're going to go
8 bankrupt. Because if you look at the number of
9 total needs that are expected in the next 15 to 20
10 years, it's going to skyrocket.

11 My question is, can biologics or
12 components of our own blood or bone marrow help
13 that? The answer is I think so. I think there's
14 a really good chance that biologic orthopedics can
15 provide transformative solutions.

16 So this is actually my MRI and my spine
17 surgeon is actually sitting in the audience here
18 today. But I underwent a discectomy about eight
19 years ago, highly successful operation. But I
20 would not like to go under the knife again. And
21 is it possible for treatments like what we're
22 talking about actually potentially avoid that?

1 The answer is yes.

2 And what do we need? In my last 30
3 seconds, we need regulatory systems that can adapt
4 to the rapidly advancing science to help take care
5 of our patients. And there are a few things that
6 are out there, and one of them is the Regrow Act.
7 It may not be perfect, but it allows for
8 expedited, you know, approval and review processes
9 that can sort of stimulate innovation and enhance
10 patient care.

11 So again, I'd like to thank the FDA, I
12 really appreciate the opportunity to speak. I'd
13 like to thank the audience and the other speakers.
14 And remind you, my little tag line, the power to
15 heal comes from within. Thank you.

16 (Applause)

17 DR. WITTEN: Thank you. Our next
18 speaker is from the Bipartisan Policy Center.

19 MS. MARCHIBRODA: Good afternoon. My
20 name is Janet Marchibroda, and I'm pleased to
21 provide comments to the FDA on behalf of the
22 Bipartisan Policy Center. The Bipartisan Policy

1 Center, or BPC, is a nonprofit organization formed
2 by former Senate majority leaders Howard Baker,
3 Tom Daschle, Bob Dole, and George Mitchell. And
4 what we do is we bring people together to
5 negotiate and find common ground on issues such as
6 economic policy, energy policy, immigration, and
7 of course healthcare. Lots of easy things to
8 focus on.

9 We commend the Food and Drug
10 Administration for holding this public hearing to
11 gain broad input on HCT -- on human cells,
12 tissues, and cellular and tissue-based products
13 and for your efforts to increase regulatory
14 clarity. Thank you.

15 BPC's advancing medical innovation
16 effort, led by former Senate Majority Leader Bill
17 Frist and former Representative Bart Gordon, we
18 made about 19 recommendations over the last year
19 to reduce the time and cost associated with the
20 discovery, development, and delivery of safe and
21 effective medical products here in the United
22 States. And we focused on a range of things

1 improving the medical product development process,
2 increasing regulatory clarity, as we're talking
3 about today, strengthening the ability for FDA to
4 meet its mission, and other issues.

5 So getting to the point, one set of our
6 recommendations that we released last year focused
7 on the need to both clarify and modernize the
8 regulatory framework for the use of human cells,
9 in many cases, one's own cells, which we've heard
10 about today, to restore healthy function in the
11 human body.

12 The science of cell therapy has evolved
13 considerably, as you well know, since 2001, when
14 Part 1271 rules were first introduced. Today, we
15 believe and many believe that cell therapies
16 represent the next generation of groundbreaking
17 treatments. It's amazing what we're seeing in the
18 field of cardiology, neurology, oncology, and
19 ophthalmology. And if you look at
20 clinicaltrials.gov and you do a sort, I guess
21 we've got like almost 5,400 clinical trials in
22 this area, over half of which are focused on

1 cancer, which is a big priority for our country
2 right now having just gotten the Moon Shot
3 Recommendations that came out. And then
4 interestingly enough, more than 100 trials are
5 focused on each of the following areas. Things
6 like heart disease, diabetes, kidney disease,
7 burns and wounds, which we've heard about. So
8 it's all very exciting. Not to mention the
9 handful of trials that are looking at issues or
10 diseases for which there is no cure, like
11 Alzheimer's Disease and Parkinson's Disease.

12 So what we did is we convened a panel of
13 nationally recognized scientists and experts over
14 the last year to inform our recommendations. And
15 many of them are with us or testifying over these
16 two days. And our goals were really twofold. To
17 enable patients to gain access in our country, not
18 flying overseas, to safe and effective therapies.
19 And then number two, to protect patients from
20 unsafe therapies.

21 And as context for our comments on the
22 four guidances, I want to just make a couple more

1 points. And this is important. I think it's
2 driving the activity that's happening in the field
3 today. Basically, there are only two pathways for
4 moving forward, as you well know. We've got
5 Section 361, the narrowly defined set of
6 treatments that we're talking about over these two
7 days. And those can be offered to patients with
8 no premarket review, as you well know, by clinics
9 that follow certain requirements. Okay, but then
10 way over here there's all other therapies, which
11 is the majority, require a full BLA and take up to
12 a billion dollars and 10 to 12 years before they
13 can be made available to patients. Even if a
14 patient's own cells are used in many cases.

15 So our recommendations, our expert panel
16 recommendations, focused on this need for a middle
17 ground pathway or a tool that the FDA could use at
18 its discretion to provide more flexibility between
19 nothing and 10 to 12 years and a billion dollars.
20 That's important context. I'm looking at my time.

21 This spring we updated our
22 recommendations in the spirit of finding common

1 ground, which we do at the Bipartisan Policy
2 Center. We listened to a handful of industry
3 organizations and patient groups who felt more
4 comfortable with not moving forward on a
5 conditional approval, but actually leveraging your
6 existing expedited programs, which a majority,
7 more than 60 percent, of drugs are actually
8 approved today under those expedited programs. So
9 we're hoping that will move forward.

10 I think the lack -- I'm watching my time
11 -- the lack of the middle ground pathway has
12 created -- you know, we've all looked, the more
13 than 500 clinics, you know, that are out there,
14 some of which may -- we don't know, there was just
15 a Google search that was performed -- may be
16 operating outside of the practice of medicine. So
17 you have that on the one hand, and then you have
18 like -- you can count on less than two hands,
19 maybe less than one hand, the number of cell
20 therapies that have been approved under
21 traditional processes.

22 I'd like to in my two minutes turn now

1 to the guidances upon which you seek input today.
2 We've got detailed written comments on all four of
3 the guidances as written. There's just one major
4 thing we want to raise. As written, the guidances
5 limit the use of adipose stem cells to the
6 underlying characteristics of the tissue in which
7 these cells are located. For example, the
8 structural support or padding and cushioning
9 against shock and fat issue. I know a number of
10 folks have raised this today. We believe the
11 current language in the guidance is inconsistent
12 with the language and intent of the definition of
13 minimal manipulation in 1271. And you've heard
14 this from many folks who have spoken today. We
15 believe that patients should have the right to use
16 their own cells for orthopedic and other
17 appropriate uses now if registered and licensed
18 clinics observe the protections included in 1271
19 without having to go through this mountainous
20 regulatory process.

21 As an aside, I also want to say for the
22 record we really like this idea of a registry that

1 a lot of folks have been talking about today.

2 Again, we plan to submit more detailed
3 written comments by your deadline. Thank you
4 again. Thank you very much for holding this
5 public hearing and for listening and giving all of
6 us the opportunity to provide constructive
7 feedback. This is a timely and important issue
8 for patients in the United States. Things have
9 changed. The science has evolved. And a flexible
10 regulatory approach that preserves the gold
11 standard, preserves the gold standard for safety
12 and efficacy and also takes into account the
13 unique aspects of cell therapies is needed to
14 support patient access to treatments that show
15 great promise for treating diseases today. Thank
16 you.

17 DR. WITTEN: Thank you. Our next
18 speaker is from the California Institute of
19 Regenerative Medicine.

20 DR. MILLS: Greetings, and thank you,
21 members of the Food and Drug Administration for
22 holding this very important meeting. My name is

1 C. Randal Mills, and it is my great honor to be
2 here today representing the California Institute
3 of Regenerative Medicine, or CIRM. CIRM is the
4 largest and most comprehensive organization
5 dedicated for the advancement of stem cell and
6 cell therapies anywhere in the world. It's a \$3
7 billion organization. We have 12 major research
8 facilities throughout the State of California, 3
9 state-of-the-art stem cell alpha clinics, a
10 genomic center, a 3,000 cell line IPS bank, and
11 over 300 projects in development from discovery
12 all the way through phase 3 clinical trials.

13 Our mission at CIRM is to accelerate
14 stem cell treatments to patients with unmet
15 medical needs. And so that's why we're here
16 today. As we see it, there are two problems that
17 exist right now. And at least the first we can
18 agree on. The first is the proliferation of stem
19 cell clinics offering treatments for which there
20 is little or no data to support safety and
21 efficacy of the therapy. The second problem is
22 the lack of progress being made through the

1 conventional biological license application
2 pathway that exists for stem cells.

3 So basically, what we're seeing is a lot
4 of what we don't want and not nearly enough of
5 what it is we do want. And we have to ask
6 ourselves why are we seeing this? And we think
7 there are two factors that are driving the current
8 situation.

9 The first -- and this can't be
10 understated -- is that patients are really
11 suffering. There is very real demand and very
12 real need that is not being met in the patient
13 community by conventional medicine.

14 The second is that the current
15 regulatory paradigm that exists is binary. It
16 exists in either an on or an off pathway. Drugs
17 can either -- specifically stem cell therapies --
18 can either come to market legally under what we'll
19 call the exemption pathway or the off pathway. It
20 takes days. There's absolutely no pre-market
21 requirements. It costs almost no money. If you
22 don't fit into that exemption, then you go through

1 the on pathway. And the on pathway couldn't be
2 further from the off pathway. It takes decades.
3 It costs billions of dollars. If you're a stem
4 cell, nothing's gotten through it. And so it's
5 this very binary pathway.

6 So the results that we're seeing today,
7 the proliferation of things going through the off
8 pathway, isn't a surprise. It's completely
9 predictable. And it's driven by two things. One,
10 a very real demand, and two, a pathway that gates
11 between these two things.

12 And I want to sort of take an
13 opportunity to create an analogy. Imagine it's
14 1903 and we're standing on the beach in Kitty
15 Hawk, North Carolina, and the Wright Flyer, the
16 first airplane, has just flown. And the FAA comes
17 along and says, hi, you don't know us, but we're
18 the FAA and we're here to help. And anyone that's
19 been in biologics knows that joke. And we're here
20 to help and here's the deal. If it looks like the
21 Wright Flyer and it resembles the Wright Flyer --
22 and we'll give you four different tests that you

1 can use -- then we'll let you develop more of
2 these airplanes as much as you want without any
3 regulation whatsoever. But if it's anything other
4 than the Wright Flyer, we're going to regulate you
5 like we're going to regulate the 787 Dreamliner.

6 That's basically what we have today. If
7 you're not willing to make a generational change
8 in a paradigm of how you're developing a cell
9 therapy, if you want to use it in -- if you want
10 to use cells to do something a little bit outside
11 of what the FDA considers homologous, it doesn't
12 step up a little bit, it steps up generationally.
13 And that's a real problem. There's a practicality
14 aspect to that. A physician can't meaningfully
15 comply with biological license application
16 regulations. They won't do it. It's an
17 impossibility for a physician working in their own
18 practice to take a cell therapy and run it through
19 the BLA pathway.

20 And so what we're here today -- I'll
21 just get to sort of the point -- is to advocate
22 for something in between. We don't like and are

1 not happy with the proliferation of these stem
2 cell clinics. But we also recognize that the
3 answer to that isn't simply by plugging the
4 loophole, basically. And the reason for that is
5 the demand that exists is very real.

6 If you imagine water running down a
7 hill, what we're trying to do here today with
8 these guidance documents is constrict the pathway
9 that that water is flowing down the hill. But the
10 water is flowing down that hill because the demand
11 or the gravity at the other side of the equation
12 is real. And so by blocking that demand, that
13 water will find a way around it. So what we're
14 asking for, we're hoping FDA will seriously
15 consider, is some alternate pathway. Don't just
16 constrict the water running down the hill, tell
17 the water where it is you want it to run. Create
18 an alternative regulatory pathway that physicians
19 and clinics and people can comply with that's
20 practical and doable and not the on or off binary
21 system that currently exists today. We think this
22 is what FDA actually intended to do when they

1 first started discussing the current regulatory
2 paradigm almost 20 years ago. And we think it's
3 good and appropriate.

4 So with that I will stop talking. And
5 thank you again very, very much for holding this
6 hearing and for taking these considerations
7 seriously. We do appreciate it.

8 (Applause)

9 DR. WITTEN: Thank you. Is there
10 someone from California Life Sciences Association?

11 DR. RAVITZ: No, I'm actually with the
12 Coalition of Wound Care Manufacturers.

13 DR. WITTEN: Okay. So next we'll hear
14 from --

15 DR. RAVITZ: Nothing like being the last
16 speaker of the day, right?

17 DR. WITTEN: We'll hear from the
18 Coalition of Wound Care Manufacturers.

19 DR. RAVITZ: Okay. My name is Karen
20 Ravitz. Good afternoon. And I am the healthcare
21 policy advisor for the Coalition of Wound Care
22 Manufacturers. The Coalition represents leading

1 manufacturers of wound care products used by
2 patients for the treatment of wounds. Our members
3 manufacture products that are included in these
4 guidance documents. Thus, the Coalition has spent
5 considerable time working with our members in
6 order to present our many concerns and
7 recommendations, with the majority of them being
8 provided in our formal written comments.

9 We thank the FDA for holding this
10 enlightening public meeting and for allowing me to
11 present our testimony. We agree with many of the
12 recommendations and comments that were provided to
13 the FDA today regarding minimal manipulation and
14 homologous use, including, but certainly not
15 limited to, the following.

16 The elimination of the term "main
17 function" from the minimal manipulation guidance
18 document and instead the agency should continue to
19 utilize the term "basic function or functions,"
20 which is already required in the regulations.

21 We request that the FDA clarify these
22 documents in order to help manufacturers clearly

1 understand the regulatory pathway. We agree that
2 examples previously provided should be put back
3 into the guidance documents. And additional
4 examples, including at what point a tissue
5 structure must be preserved to be considered
6 minimally manipulated, should be placed into these
7 documents to provide additional clarity.

8 We believe that the recommendation that
9 was stated today regarding providing flowcharts to
10 demonstrate the evaluation of products would also
11 be helpful.

12 We also agree that the change regarding
13 how minimal manipulation is determined and
14 specifically the focus on the main function of the
15 tissue in the donor rather than by the function of
16 the tissue in the recipient is problematic. The
17 analysis should be based on the effects that the
18 processing has in the tissue's utility for
19 reconstruction, repair, or replacement in the
20 recipient.

21 We also heard that the FDA had stated in
22 the past that amnion may be used for wound healing

1 when cytokines are present, meaning that it's not
2 decellularized. We agree with this statement and
3 urge the FDA to continue to permit amnion in their
4 homologous use considerations.

5 Several presenters stated that
6 extracellular matrix signals evoke recipient cell
7 responses, which suggests that structural tissues
8 have basic functions beyond physical support
9 and/or protection. We agree with this argument.

10 And finally, we agree with the following
11 two recommendations: that the FDA expressly
12 acknowledge that some tissues have both structural
13 and nonstructural functionality, and that the FDA
14 provide scientific explanations of different
15 applications of minimal manipulation. These
16 recommendations highlight our most important
17 issue, which is the process that the FDA has used
18 in issuing these guidance documents, especially
19 the guidance on minimal manipulation.

20 We believe that these types of documents
21 serve as guidance to interested parties. The
22 purpose of a guidance document is to allow the

1 industry to know what the FDA's current thinking
2 is on a topic. There are regulations that are
3 issued with respect to the specific topics of
4 these draft guidance documents that should not be
5 in conflict with the guidance itself. The
6 guidances should provide clarity to the
7 regulations. They should not be adding new
8 requirements to the regulations, which we believe
9 is what these guidance documents do.

10 Too often the FDA issues guidance
11 documents that makes substantive policy changes
12 without going through the appropriate notice and
13 comment period. A concern not only to those in
14 the industry, but also to members of the Senate
15 Committee on Health, Labor and Education, or
16 Education and Labor. These documents fit into
17 this category. For instance, given the expanded
18 definition of "minimal manipulation" to reply upon
19 the main function in order to determine whether a
20 tissue type is considered structural or
21 nonstructural imposes new limitations under the
22 current regulation and are considered substantive

1 changes. As such, this draft guidance should have
2 been issued in accordance with a notice and
3 comment proceedings required by the Administrative
4 Procedures Act, or the APA.

5 Section 553 of the APA requires the
6 publication of proposed agency rules be followed
7 by a period of time for consideration and comment
8 by the public. A notice and comment period is not
9 required if an agency issues an interpretative
10 rule or a general statement.

11 These guidance documents are not an
12 interpretive rule, nor are they a general
13 statement. Rather, they contain material changes
14 to existing regulation with additional
15 requirements being imposed. Case in point with
16 the examples provided all day today regarding the
17 new term "main function" and the material change
18 in how minimal manipulation is determined and
19 specifically the focus on the main function of the
20 tissue and the donor rather than the recipient.

21 The Coalition recommends that the FDA
22 work with interested stakeholders. This meeting

1 was a first good step, and as a result, throughout
2 the day the FDA has been provided with many great
3 recommendations regarding these documents, which
4 we hope you adopt.

5 We also recommend that the FDA take one
6 of two steps moving forward. Either the FDA
7 should eliminate the substantive policy changes
8 from these guidance documents and continue to work
9 with stakeholders to provide additional examples
10 and clarity to the HCTP guidance documents or, if
11 the FDA wants to make substantive changes, they
12 should withdraw these guidance documents and
13 instead go through the appropriate regulatory
14 process.

15 Whether the FDA maintains the current
16 guidance documents with added clarifications
17 provided or whether substantive changes are
18 proposed within the appropriate regulatory
19 process, we hope that the FDA seriously considers
20 the recommendations made here today by the many
21 organizations that provided testimony. Thank you
22 for your time.

1 DR. WITTEN: Thank you. I'll now ask
2 the panel if they have questions for the speakers.

3 MS. ZAVAGNO: I have a question for Dr.
4 Allan Mishra.

5 DR. WITTEN: Speak into the mike.

6 MS. ZAVAGNO: I'm wondering if you can
7 explain to me why you think blood is not a drug?
8 That was a big part of your presentation.

9 DR. MISHRA: Yes. I think it's a
10 paradigm shift. So if we think of drugs as
11 manufactured products or chemical-derived products
12 that we distill from plants or make them in big
13 bioreactors, that's a drug. If I think of your
14 blood, it's an incredibly complex system of
15 hundreds of proteins that are natural to you. And
16 to me that is not a drug. So that's where I'm
17 parsing it in a different paradigm perhaps than
18 the FDA. But I don't think of it -- I don't think
19 of myself as being -- as drugs flowing through my
20 body right now. I think of blood flowing through
21 my body.

22 MS. ZAVAGNO: You are aware that blood

1 is a licensed product, right, by the FDA? I just
2 wanted to point that out. And I also wanted to
3 point out or ask you if you were familiar with the
4 definition of an HCTP, which is --

5 DR. MISHRA: I am, and I --

6 MS. ZAVAGNO: -- blood and blood
7 components.

8 DR. MISHRA: I again appreciate the
9 opportunity to speak here. I utilized my eight
10 minutes perhaps not in exactly the way that was
11 described, but I utilized it because I feel very
12 passionate about -- perhaps some of the other
13 speakers were more eloquent than I was about a
14 paradigm shift or a need for a middle pathway in
15 terms of how we regulate biologic products,
16 whether it's blood, bone marrow, or adipose
17 tissue. The water analogy is a fantastic one. If
18 any one of you or anyone in this room who's not a
19 clinician followed us around, it is not a trickle,
20 it is a waterfall of a problem, an avalanche of
21 snow coming down the mountain that we are not
22 adequately prepared for.

1 And frankly, as Americans, we're not
2 really treating it like an emergency. And I
3 didn't realize that until this summer when I met
4 Captain Chaby, and I realized our veterans are
5 coming back and they're seeking out some of these
6 regenerative medicine products because they're
7 dissatisfied, as we are, with what's available.
8 And I don't think we can iteratively consider
9 options. I think we need to consider this almost
10 an emergency in terms of how we can perhaps light
11 a fire under all of us to say we can't just talk
12 about this for another 2 years, 5 years, or 10
13 years. And we don't have the money as clinicians
14 to do a BLA.

15 And I was actually blocked by an IRB
16 because we had to go to the FDA to get your
17 blessing to do a study. And it was an enormous
18 challenge to figure out if we could marshal the
19 resources to determine whether we needed your
20 approval or not.

21 So what you do is incredibly important
22 and incredibly impactful for those of us at the

1 vanguard of trying to develop new products for our
2 patients. Because what we have right now, it
3 doesn't even always work as well as we want it to.
4 And it's going to drive us into bankruptcy if we
5 don't come up with better solutions for the
6 problems that I'm facing every day in my clinic.

7 MS. ZAVAGNO: All right. Thank you.

8 DR. MISHRA: Thank you. (Applause)

9 DR. ANATOL: I have two questions for
10 ARM. So I'll start with what I think is the easy
11 question first. You referred to the guidances
12 needing some clarity around product
13 characterization. Can you give a little bit more
14 detail? Like I'm not sure if you were referring
15 to processing steps or something else.

16 DR. WERNER: Well, I think what we were
17 talking -- that was in the context of that we
18 represent folks who are trying to do research and
19 develop products across the spectrum, right? And
20 how FDA defines certain of these key terms will
21 determine how they're classified. So perhaps
22 classification is a better word than

1 characterization in this context. But that's what
2 I was referring to.

3 DR. ANATOL: Okay. And then -- thank
4 you. You also suggested that we provide more
5 examples. I think both around minimal
6 manipulation and homologous use. Do you have
7 specific examples in mind?

8 DR. WERNER: In our written documents we
9 do.

10 DR. ANATOL: Okay.

11 DR. WERNER: Yeah.

12 DR. ANATOL: Thanks.

13 DR. WERNER: And we have the sample flow
14 -- people talked about -- we talked about
15 flowcharts. We have samples of those, too.

16 DR. ANATOL: Okay. Great. Thanks.

17 DR. WERNER: Mm-hmm.

18 DR. WITTEN: I have a question for the
19 speaker from AABB. In your talk you requested a
20 number of things, I think, related to the guidance
21 documents. Thank you for commenting on the
22 guidances. And one was more examples of

1 nonstructural versus structural tissues. And you
2 provided a couple of examples of tissues. But it
3 wasn't clear what -- do you have a viewpoint on
4 that, or do you have recommendations or some
5 examples that you'd like to suggest we consider as
6 examples to provide clarity about structural and
7 nonstructural tissue?

8 DR. KAMANI: Well, there are two points
9 we are trying to make. One is that the list needs
10 to be more comprehensive so that at least those
11 tissues that are tissues and cells that are being
12 collected currently either for the purpose of
13 storage or manipulation are at least included in
14 those lists. And secondly, it's not clear because
15 the guidance is silent on a couple of those
16 tissues whether it would belong to one category or
17 the other. And the example we chose was cord
18 tissue, which currently is being stored by a
19 number of facilities for the purpose of future use
20 as a source of mesenchymal stromal cells. And the
21 other is tissue such as the thymus gland or thymic
22 tissue, which occasionally is used for

1 transplantation.

2 DR. WITTEN: Okay, thanks, that's
3 helpful. Other questions from panel members?

4 MR. WEINER: I had one question, if I
5 could. I think it was the Alliance for the
6 Advancement of Cellular Therapies. I just wanted
7 to clarify something on your -- as I understood
8 your talk, it sounded like you were giving a
9 detailed proposal for how registries might be used
10 to augment phase 2 data.

11 DR. MILLER: Yes.

12 MR. WEINER: And probably with regard to
13 lack of sufficiently powered data. And walking
14 through it all, I was just curious how you'd
15 consider your proposal to compare to sort of a
16 more typical through a phase 4 approach to getting
17 additional data for post market.

18 DR. MILLER: I think there is an analogy
19 at a post marketing surveillance. I mean, that's
20 really what you're saying. There's a product
21 that's out there. We believe it's able to be used
22 and commercialized, and yet you want a much more

1 in-depth look at the safety and efficacy that's
2 proven in subsequent analysis. And I think this
3 is getting out of the clinical trial and the rigor
4 of that where sometimes you're excluding a lot of
5 patients that would be not qualifying by that
6 protocol criteria that would really enhance the
7 knowledge of the overall applicability of a
8 specific cell therapy or strategy to a wider
9 number of patients.

10 MR. WEINER: Thank you.

11 DR. MILLER: Yep.

12 DR. WITTEN: Okay, before we close, I
13 have two announcements to make. One is, for those
14 of you who are returning tomorrow -- and I hope
15 that and encourage people to do so -- please bring
16 your badge again, it will simplify things. So
17 bring your badge back. And the second is that
18 some woman's jewelry was found in the women's
19 bathroom. If you have lost an item, you can
20 retrieve it from the NIH library. So that's just
21 for anybody who's lost something.

22 So now, just to close, I'd like to thank

1 everyone, the speakers for their presentations and
2 the audience, whether in person or by webcast, for
3 your attention in today's meeting on behalf of the
4 FDA panel. We had a very full day of interesting
5 and insightful comments. Along with the comments
6 of the dockets, we'll consider these as we
7 finalize the guidances.

8 The hearing is concluded for today and
9 will reconvene tomorrow at 9:00 a.m. Thank you
10 for your participation.

11 (Whereupon, at 4:21 p.m., the
12 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

