BIPARTISAN POLICY CENTER

September 27, 2016

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061 (HFA-305)
Rockville, MD 20852

Re: Draft Guidances Relating to the Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (Docket No. FDA-2015-D-3719)

Dear Sir or Madam:

The Bipartisan Policy Center (BPC) is pleased to provide comments on the Food and Drug Administration's (FDA) draft guidances related to the regulation of human cells, tissues, and cellular and tissue-based products (HCT/Ps).

BPC is a non-profit organization that drives principled and politically viable solutions through rigorous analysis, painstaking negotiation, and aggressive advocacy. Current areas of focus include health, energy, national and homeland security, the economy, housing, immigration, infrastructure, and governance.

BPC's Health Innovation Initiative conducts research and engages experts and stakeholders to advance policies that improve health and health care for Americans. Through its *Advancing Medical Innovation* effort—led by former Senate Majority Leader Bill Frist, MD and former Congressman Bart Gordon—BPC is advancing policies that promote medical innovation and reduce the time and cost associated with the discovery, development, and delivery of safe and effective medical products for patients in the United States. In 2015, BPC released the report, Advancing Medical Innovation for a Healthier America, which contains 19 recommendations to improve the medical product development process, increase regulatory clarity, strengthen the ability for FDA to carry out its mission, and increase investments in medical products that address unmet and public health needs. One of those recommendations focused on the need to both clarify and modernize the regulatory framework for the use of human cells—in many cases, one's own cells—to cure disease and restore healthy function in the human body.

The science of cell therapy has evolved considerably since 2001 when the FDA first created a regulatory structure for HCT/Ps. Today, cell therapies represent the next generation of groundbreaking treatments, showing enormous promise in the areas of cardiology, neurology, oncology, and ophthalmology. Thousands of clinical trials are now underway that are focused on cancer, heart disease, urologic diseases, kidney disease, trauma-related burns and wounds, and diabetes. A number of trials are also underway to address diseases for which there is no cure, such as Alzheimer's, MS, and Parkinson's disease.

Today, there are only two pathways to bring these life-saving therapies to patients in the United States. Under current law, a very narrowly defined set of HCT/Ps—regulated under section 361 of the Public Health Service Act—can be offered to patients with no pre-market review by clinics that follow requirements of 1271. All other HCT/Ps—those regulated under section 351 of the Public Health Service Act—are treated like drugs. They require a full Biologics Licensing Application (BLA) and take up to $1 billion and 10 to 12 years before they can be made available to patients—even if a patient's own cells are used. In other words, only two extremely different outcomes are available—there is no "middle ground." As a result, since 2001 when the regulatory structure for HCT/Ps was created, only a handful of cell therapies have been approved by the FDA.

The current regulatory approach has resulted in where we are today, which is the proliferation of hundreds of clinics offering cell therapy treatments in response to growing consumer demand—some of which may fall outside of the practice of medicine—and virtually no approvals of cell therapy-based products given the high hurdle needed to get there. As a result, American companies are increasingly making their investments in these innovative products in other parts of the world—including Europe and Japan—where new regulatory pathways have already been implemented, as opposed to here in the U.S.

Last year, BPC convened a panel of nationally recognized scientific and academic experts to inform our recommendations for modernizing the way that cell therapies are regulated. Our goals were two-fold: (1) to enable patients to gain access to safe and effective cell therapies here in the United States and (2) to protect patients from unsafe therapies.

Our recommendations focused on the need for a middle ground pathway that would provide FDA with more flexibility with regard to the way that it regulates cell therapies. This middle ground pathway would exist between section 361—which requires no pre-market review—and section 351—regulation that is akin to that used for drugs. This spring we updated our recommendations in the spirit of finding common ground based on additional input received from a handful of industry organizations and a small group of patient organizations. In short, we called for clarifying FDA's authority to use its existing expedited programs (under which a majority of drugs have been approved since 2014) for approval of cellular and regenerative therapies.

The creation of a middle ground pathway will give FDA the discretion to utilize existing expedited programs to bring both safe and effective cell therapy treatments to patients, here in the U.S., and improve our nation's global competitiveness.

Finally, the use of registries—common in other medical specialties—in the field of cell therapy could provide safety and outcomes data to support transparency and provide useful information for patients, inform clinical decision-making, guide reimbursement decisions, and support regulatory decision-making.

Our specific comments on the following four guidances are summarized in Attachments I, II, III, and IV.

- Draft FDA Guidance: *Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products*, October 2015
- Draft FDA Guidance: *Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations,* December 2014
- Draft FDA Guidance: *Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products*, December 2014
- Draft FDA Guidance: *Same Surgical Procedure Exception Under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of Exception*, October 2014

A high-level summary of those comments is provided below.

Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products

- The regulatory definition of "homologous use" that allows application of §1271 is broad (e.g., use of cells that perform the same basic function or functions in the recipient as in the donor). Again, the cited examples referenced by FDA are unnecessarily narrow.

- Infusion of hematopoietic stem cells to treat blood disorders is given as an example of homologous use, but infusion intravenously to differentiate into neuronal cells to treat cerebral palsy is given as an example of non-homologous use even though those cells have this demonstrated capability. (Actually the use of cord blood cells for CP is not based on differentiation into healthy nerve cells but documented paracrine signaling to reduce inflammation and promote neural connectivity.) If these cells possess the biological characteristics to proliferate, differentiate and reduce inflammation, FDA has the discretion to accept evidence that these blood borne stem cells perform the same function in the donor as in the recipient.

- Less obvious examples should be included in the guidance where FDA has permitted tissue or stem cell uses as homologous other than the most obvious ones included; e.g., highlight the uses of amniotic cells or tissues in the eye to treat corneal defects, ocular inflammation, or wound healing, rather than limit examples to skin grafts or heart valve replacements.

See Attachment I for BPC's more detailed comments.

Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations

- Issuance of this guidance specific to use of adult stem cells derived from fat tissue seems designed to stop any continued use of cell therapy under §1271 without submission and approval of an FDA premarket approval application.
- The guidance notes that processing to isolate non adipocyte or non-structural components from adipose tissue (with or without subsequent cell culture or expansion) is MMM because it alters the original relevant characteristics relating to the tissue's utility for reconstruction, repair or replacement (Guidance at pg. 3).

- As noted in the discussion of the Minimal Manipulation Guidance above, FDA again intentionally combines the MM definition of cell processing with processing of the underlying structural tissue which is not part of the product being developed. This runs completely counter to the construction of the regulatory language of §1271.3(f).

- It is legally inappropriate and a misreading of the regulation (§1271.3(f)(2) v. (f)(1)) to deem MSCs isolated from adipose tissue as MMM based on the characteristics of the tissue from which these cells are removed. The standard for MM of cells is whether the processing alters the relevant biological characteristics of the cells ((f)(2)), not whether the processing alters the tissue's utility for reconstruction, repair or replacement ((f)(1)).

- Use of adipose tissue or adipose-derived MSC for breast augmentation should be considered homologous, not used as an example of non-homologous use because of the narrow determination that breast tissue is not fat tissue, but tissue to produce milk (lactation) after childbirth.

- The draft guidance states that if stem cells are isolated from lipoaspirate, the adipose tissue would no longer be considered HCT/P. Therefore, in FDA's view, even if these cells are injected into the same patient, the "same surgical procedure exception" under §1271.15(b) would not apply (Guidance at pg. 8).

- Again, FDA confuses the manipulation and use of the cells under §1271.3(f)(2) from use of the underlying tissue under §1271.3(f)(1).

- There is no legal authority, of which we are aware, to determine that stromal MSC or other cells derived from adipose tissue are not HCT/Ps. HCT/Ps are defined broadly as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient" (1271.3(d)).

See Attachment II for BPC's more detailed comments.

Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products

- FDA should view extraction or separation of cells independently from the underlying function of the structural tissue, where the cells are the intended product and not the tissue from which they are harvested.

- The §1271 definition of "minimal manipulation" (MM) provides FDA with this important tool to evaluate cells independently as minimally manipulated if processing "does not alter the relevant biological characteristics of cells" (1271.3(f)(2)).

- It should be irrelevant scientifically and legally if, for example, use of these cells is not related to the relevant characteristics of fat tissue to pad and cushion against shocks (the tissue and not the cell criteria), if the cells have the inherent biologic characteristics of being able to differentiate and proliferate when isolated—the value of stem cells in restorative medicine.

- Limiting the allowable use of stromal/stem cells to the characteristics of the tissue in which they are stored is contrary to the language of the regulation and its format which includes a separate definition of minimal manipulation for cells and structural tissue.

- The cell definition should be used if cells are the intended product (e.g., does processing alter the relevant biological characteristics of the cells). The structural tissue definition should be used if the tissue is the intended product (e.g., does processing alter the tissue's utility, for reconstruction, repair or replacement).

- The Guidance should focus on whether the extraction, processing, separation, or other manipulation of the tissue/cells increases the risk of infection or introduction of substances with unproven safety profiles into the patient.

- FDA seems to intentionally eliminate the utility of stromal/stem cells under §1271 regardless of the techniques used to isolate and process those cells by requiring that extraction or separation of cells from structural tissue is considered more than minimal manipulation (MMM) if removal reduces the bulk of the adipose (fat) tissue from which they are extracted (Guidance, pg. 8, Example 10-1).

- This interpretation is contrary to the language and intent of the regulatory definition of minimal manipulation.

- In Section C of the draft guidance, FDA differentiates between obtaining a higher concentration of hematopoietic stem/progenitor blood cells using a mobilized peripheral blood apheresis product which it deems minimally manipulated, and incubating selected placental/umbilical cord blood cells in a laboratory vessel containing culture media and/or growth factors to achieve a large number of cells capable of long-term repopulation of bone marrow as more than minimally manipulated (because the processing theoretically may affect production of intracellular or cell-surface proteins and other markers) which likely have little or no significance in the clinical outcome.

- The science in the field, or the regulatory definition of minimal manipulation, does not require FDA to take such a narrow or restrictive "either-or" approach. FDA could more generally determine simply that the relevant biological characteristics of cells include the ability to divide, expand and proliferate. Since cells contain the ability to reproduce and proliferate, allowing them to do so naturally in a supportive medium arguably does not alter their relevant biologic characteristics to divide or proliferate.

- Simply taking a small step back in its regulatory interpretations, when justified by established existing science, could make use of these blood stem cells much more effective, for example, in treating blood cancers, and improve public health.

See Attachment III for BPC's more detailed comments.

Same Surgical Procedure Exception Under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of Exception

- The Guidance is intended to clarify the application of §1271.15(b) that exempts procedures from §1271 if an establishment removes HCT/Ps from an individual and implants "such HCT/Ps" back into the same individual during the same surgical procedure.

- The Guidance, not the regulation, interprets "such HCT/Ps" to mean that they are in their original form (Guidance, footnote 4, pg. 3). This interpretation deviates from the MM standard with FDA stating that the HCT/P can only be "rinsed, cleaned, sized or shaped" to qualify for the same surgical procedure exception, and cells cannot be removed from host tissue.

- This discussion creates inconsistencies between the MM standard that permits extraction and isolation of stem cells from underlying tissue by further denying use of such cells without drug or device approval even if autologous, homologous, MM stem cells are implanted in the same surgical procedure.

- The limited examples involve only tissue transfers not cells (e.g., skin grafting and coronary bypass surgery)(Guidance at pg. 4). Examples of the same surgery exception should be applied to a narrow use of stem cells (e.g., hematopoietic stem cell transplants to treat blood borne disease, etc.).

See Attachment IV for BPC's more detailed comments.

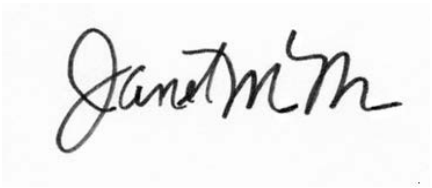
Thank you for the opportunity to participate in your public hearing held on September 12-13, 2016, and for providing us the opportunity to provide constructive feedback on regulations associated with cell therapies.

This is a timely and important issue for patients in the United States. A flexible regulatory approach that preserves the gold standard for safety and efficacy and also takes into account the unique aspects of cell therapies is needed to support patient access to treatments that not only treat common orthopedic injuries and wounds, but also show great promise for treating diseases such as cancer, heart disease, and neurological diseases such as Parkinson's disease and Alzheimer's.

We look forward to continued engagement with FDA and supporting your efforts to improve upon current regulations associated with cell therapies.

If you have any questions or wish to discuss BPC's comments, please contact me at 202.379.1634 or jmarchibroda@bipartisanpolicy.org.

Sincerely,



Janet M. Marchibroda
Director, Health Innovation Initiative

Attachments

Attachment I
Bipartisan Policy Center Comments
FDA Draft Guidance - *Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products*

FDA Guidance Provision	Comment	Rationale
FDA's definition of "homologous" for purposes of applying either 361 (1271) or 351 (full BLA) is: the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P **that performs the same basic function or functions in the recipient as in the donor** (21 CFR §1271.3(c)) HCT/P (as regulated solely by 361) is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent (§1271.10(a)(2))	This regulatory standard is broad enough to incorporate the fundamental properties of stem cells, e.g. their ability to self-renew, as well as proliferate and differentiate into lineage-committed functional cells to help achieve or restore the same or similar functions in the recipient as in the donor. Instead, FDA opted to interpret this flexible standard so narrowly that the use of most, if not all, differentiating stem cells (e.g., mesenchymal from stroma or adipose tissue, hematopoietic, embryonic or induced pluripotent) is deemed non-homologous Standard should not be the cell function in the tissue or location in which it is identified, but the function or characteristics of the cells themselves. They should be deemed homologous under this standard if they help achieve or restore the same or similar function in the recipient as in the donor	This broader interpretation would permit the safe and documented restorative benefits of stem cells with all the protections that exist under the 1271 regulations.

FDA Guidance Provision	Comment	Rationale
	FDA should also view the European Medicines Agency reinterpretation by viewing not the original function of these cells, but whether they are used in "the same anatomical or histological environment"	
Stated examples of homologous use include recipient cells that are identical to donor cells (e.g., skin for skin); or non-identical cells that perform one or more of the same basic functions in recipient as in donor Heart valve replacing heart valve; or Pericardium to repair or reconstruct dura matter and serve as wound covering (Guidance at 3-4)	The stated examples are the most narrow and most obvious and also typically utilized in a "same surgical procedure" situation. FDA alone knows the specific facts and circumstances of HCT/P uses that it has determined to be homologous. Broader and more far reaching examples should be provided, not merely the narrowest and most obvious examples. For example we are aware of a homologous determination made for the use of amniotic membrane tissue for use in healing corneal erosion (*see* Protera-BioTissue)	
Not homologous if HCT/Ps "for use as an unproven treatment for a myriad of disease conditions." (Guidance at 4)	This states the obvious and is not helpful.	

FDA Guidance Provision	Comment	Rationale
Examples cited for homologous "repair, reconstruction, replacement, or supplementation of recipient's cells or tissues" include implantation of dermal matrix into facial wrinkles, or use of bone chips to supplement bony defects.	The Guidance should be broadened to identify permitted use of differentiating stem cells for which ample research exists to demonstrate use to restore the same of similar functions in the recipient as in the donor.	
Likewise, FDA states that "[i]t is not necessary for the HCT/P in the recipient to perform all of the basic functions it performed in the donor" to meet the definition of homologous use, but any basic function that the HCT/P is expected to perform in the recipient must be a basic function that the HCT/P performed in the donor. (pg. 4-5). The example given for homologous use was the use of hematopoietic stem/progenitor cells (HPC) for disorders affecting the hematopoietic system because the peripheral blood product performs the same basic function of reconstituting the hematopoietic system in the recipient. Cord blood HPCs infused intravenously to differentiate into neuronal cells for treatment of cerebral palsy were given as an example of non-homologous use because of "insufficient evidence to support that such differentiation is a	FDA is again using unreasonably narrow examples to deny 1271 treatment for technologies that have been proven safe and effective. For example, clinicians generally agree that the mechanism of action for the use of HPCs for blood reconstitution is well known and well characterized. This mechanism of action involves engraftment, massive cell proliferation and differentiation. That scientific evidence includes: *in vitro* cell cultures demonstrating that progenitor cells can grow and differentiate; animal models following lethal radiation demonstrated rescue with bone marrow or ever highly purified cells given by IV where blood cell counts eventually recover to normal levels. Human studies using genetic marking show that new blood cells are derived from donor stem cells. Stem cell studies for cardiac repair have demonstrated direct differentiation,	

FDA Guidance Provision	Comment	Rationale
basic function of these cells in the donor."	fusion, reduced inflammation, stimulation of endogenous repair and improved blood flow. It is likely that cell therapy produces a combination of these effects based on the specific clinical situation. One of the advantages of cell therapy over drugs is the 'intelligence' of the cell and it's ability to assess, adapt to and respond to specific signaling in damaged tissue. In the case of using cord blood cells for CP, there is no expectation of neuronal differentiation or integration. Rather, the monocytes in cord blood have been documented to act through paracrine signaling to reduce inflammation and promote neural connectivity. Finally, dozens of human clinical studies have documented the use of regulatory T-cells as adaptive cell therapy for the prevention of graft v. host disease (GVHD) in human transplant patients. If these cells or tissues possess the characteristics to proliferate and differentiate, FDA has the discretion to opine that these characteristics allow	

FDA Guidance Provision	Comment	Rationale
	them to perform these functions in the donor or the recipient.	
The basic function of a corneal graft transplanted to restore sight is a homologous use, but amniotic membrane used for bone tissue replacement to support bone regeneration is not a homologous use.	In addition to the example of a non-homologous use of amniotic membrane, the Guidance should be modified to include a homologous use of this tissue (e.g., use in healing corneal erosion (*see* Protera-BioTissue)	
A HCT/P may perform the same basic function even when it is not used in the same anatomic location where it existed as a donor. Use of an acellular dermal product for supplemental support, protection, reinforcement or covering for a tendon was given as an example of a homologous use, while use for tendon replacement or repair was non homologous. Also use of amniotic membrane for wound healing of dermal ulcers was non-homologous.	In addition to the example of a non-homologous use of amniotic membrane, for example, the Guidance should be modified to include a homologous use of this tissue (e.g., use in healing corneal erosion (*see* Protera-BioTissue) Furthermore, if FDA could modify its position to consider the function of the cell or tissue, regardless of location, use of amniotic membrane for wound healing should be considered homologous.	

Attachment II
Bipartisan Policy Center Comments
FDA Draft Guidance - *Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations*

FDA Guidance Provision	Comment	Rationale
Draft guidance reportedly issued because "FDA has recently received numerous inquiries regarding HCT/Ps manufactured from adipose tissues."	Most of those inquiries likely involved discovery and use of mesenchymal stromal cells (MSCs) which are located within the structure of adult fat tissue. The primary purpose of the guidance seems directed specifically to "slam the door" concerning the use of MSCs without development of a full drug/biologic application under §351 PHSA. Issuance of such guidance pushes U.S. patients further behind in realizing the therapeutic value of MSCs in safely treating disease. Such unreasonably narrow definitions also ignore existing science and strip the Agency of an important regulatory tool under §361 PHSA used so effectively to use stem cells to treat blood-borne disease. This FDA position will establish a precedent that will affect MSCs derived from all other tissue, such as bone marrow, cord tissue, amniotic fluid, etc. It would be more scientifically valid to	BPC and many clinical experts involved in regenerative medicine believe that the mechanisms used by FDA for new drug development are: (1) unnecessary to guarantee safe and effective use, (2) outdated; and (3) not tailored to the use of adult stem cells.

FDA Guidance Provision	Comment	Rationale
	consider the methods of manufacturing MSCs derived from these tissues and assigning the regulatory pathway accordingly. Autologous MSC cells derived from a direct processing method using FDA approved reagents, and administered in the same surgical procedure, or within a few days of initiation of manufacturing, should be regulated under 361. Autologous or allogeneic cells manufactured with complex methods (e.g., more than minimal manipulation) should be regulated under 351.	
Processing to isolate non-adipocyte or non-structural components from adipose tissue (with or without subsequent cell culture or expansion) is generally considered more than minimal manipulation—because the adipose tissue are entirely removed from the non-adipocyte or non-structural isolates, thereby altering the original relevant characteristics relating to the tissue's utility for reconstruction, repair, or replacement (Guidance at pg. 3). .	In adopting this narrow interpretation, FDA is deviating unnecessarily from the plain meaning of its own 1271 regulation. In the definition of "minimal manipulation" (§1271.3(f)), FDA properly focused on whether the intended product was a cell or the underlying structural tissue. Only if the focus was on the adipose tissue itself, for example, then the requirements of §1271.3(f)(1) applied "that the processing should not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement."	When processed under the other limitations of the HCT/P regulatory framework in 1271, the use of these stem cells is safe and effective (e.g., minimally manipulated, homologous use, no combination with other prohibited articles, autologous use, or allogeneic in relative, etc.). FDA should follow its own regulations without linking MSCs to the structural adipose tissue in which they are located and isolated.

FDA Guidance Provision	Comment	Rationale
	However, where the intended product is the MSC/ stromal stem cells, §1271.3(f)(2) applies related to cells, not §1271.3(f)(1) related only to structural tissue. The cell provision in §1271.3(f)(2) applies a different standard; that the processing "does not alter the relevant biological characteristics of the cells." If those MSCs have the biological ability to differentiate and proliferate, it should be minimal manipulation to isolate them and allow them to use these inherent biological characteristics.	
It is more than minimal manipulation to isolate adipose-derived stromal/stem cells from adipose tissue for clinically therapeutic uses. This processing breaks down and eliminates the structural components of this tissue that function to provide cushioning and support thereby altering the original relevant characteristics of the HCT/P relating to its utility for reconstruction, repair and replacement. (Guidance at pg. 4)	As noted above, this cited criteria is limited to use of the structural adipose tissue itself, and not MSC cells isolated from this tissue, that are the intended product for human use.	Rather than using non-binding guidance to prevent the use of stem cells in regenerative medicine under 1271, FDA should acknowledge the state of the science in this regard and permit this narrow use in these safest of circumstances.
In contrast, processing that does not affect the adipose tissue's utility as a structural tissue for reconstruction,	This example should be limited to §1271.3(f)(1) when the structural adipose tissue itself is the product intended for	

FDA Guidance Provision	Comment	Rationale
replacement, or repair may be considered minimal manipulation (e.g., aliquoting, rinsing, removal of macroscopic debris, and freezing). (Guidance at pg. 4)	patient use, or when a cell-containing tissue is the intended product.	
Use of adipose tissue to cosmetically fill void in the subcutaneous space in the face or hands is homologous use because of its use to support the subcutaneum.	This obvious and narrow example of homologous use should not preclude use of MSCs isolated from adipose tissue if the tissue itself is not also retained for therapeutic use. The homologous definition focuses on whether the cells, or tissue, "perform the same basic function in the recipient as in the donor."	
Breast augmentation would generally be considered non-homologous use because the basis function of breast tissue is to produce milk (lactation) after childbirth.	Use of adipose tissue and MSCs for breast reconstruction is now a common clinical practice. When considering that the breast is largely composed of fat tissue, and that the breast has many functions other than lactation, applying fat-based HCT/Ps to restore breast shape should be considered homologous use.	
If stem cells from the lipoaspirate are isolated, the adipose tissue would no longer be considered HCT/P. Thus, even if these cells are injected into the same patient from which they are removed	FDA confuses use of the isolated cells themselves from use of the underlying tissue in which these cells re harvested. MSCs are unique in that they do not undergo lineage differentiation in fat	The plain language of FDA's definitions of minimally manipulated and homologous contained in §1271.3(c) and (f) allow use of cells for purposes apart from the function of the tissue in which they are

FDA Guidance Provision	Comment	Rationale
during the same surgical procedure, the exception under §1271.15(b) [for use during the same surgical procedure] would not apply. (Guidance at pg. 8)	tissue. They may have another function in this tissue, but it is currently unknown. Yet, they possess the biologic characteristics to reproduce and differentiate into other types of cells if isolated and relocated throughout the body. They also act as effector/signaling cells exerting anti-inflammatory and immune tolerance effects in vivo. These uses should be considered a homologous use of these cells.	located.

Attachment III
Bipartisan Policy Center Comments
FDA Draft Guidance - *Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products*

FDA Guidance Provision	Comment	Rationale
Extraction or separation of cells from structural tissue in which the remaining tissue's relevant characteristics relating to reconstruction, repair, or replacement remain unchanged generally would be considered minimal manipulation. (Guidance at 5; Proposed Establishment Registration and Listing Rule 63 FR 26744, 26748)	FDA should view extraction or separation of cells independently from the underlying function of the structural tissue where the cells are the intended product and not the tissue. Here FDA is incrementally laying the foundation to deem extraction of stromal or mesenchymal stem cells (MSCs) from adipose tissue as more than minimally manipulated (MMM) if removal reduces the bulk of the adipose (fat) tissue from which they are extracted. The real issue here is whether the extraction, processing, separation, or other manipulations of the tissue/or cells is associated with increased risk for infection or introduction of substances with unproven safety profiles in the patient. Routes of administration also may influence this designation. A cell administered into a subcutaneous space in a joint carries less risk than that same cell administered into the brain or spinal fluid. In general, the evaluation of the	The relevant regulation defining minimal manipulation (MM) clearly separates structural tissue processing from the processing of cells. MM of cells is defined simply as "processing that does not alter the relevant biological characteristics of cells…"21 CFR 1271.3(f)(2). The MM determination for the underlying structural tissue from which the cells are extracted is treated separately in 1271.3(f)(1) as "not alter[ing] the original relevant characteristics of the tissue relating to the tissues utility for reconstruction, repair or replacement." Since stromal and MSCs located in adipose tissue are not related to the relevant characteristics of fat tissue to pad and cushion against shocks (including its bulk and lipid storage capacity), their extraction should not be deemed MMM if the cells are the intended product and not the fat tissue. The term MMM should focus exclusively on whether the extraction, separation and processing of

FDA Guidance Provision	Comment	Rationale
	route of administration should be risk based. For manufacturing, if the cells are prepared in a clean room and only exposed to reagents that are FDA approved for human use, qualification to manufacture should not require requalification or validation of these reagents. On the other hand, if reagents that are not approved for human use are used in manufacturing, a more rigorous qualification of the process will be required.	the cells themselves alter their relevant biological characteristics (e.g., ability to proliferate, differentiate, etc.)
FDA states that if you isolate cells from structural tissue, you should apply the MM definition of the underlying structural tissue and not the cells themselves. Guidance at 8, Question 10.	This combination of cells with the structural tissue from which they are extracted allows FDA to determine that removal of stromal and MSCs from adipose tissue is MMM because, in FDA's view, removing cells alters HCT/Ps ability to provide padding and cushioning. Example 7-3, Guidance at 6, Q-7.	This interpretation is unnecessarily narrow. It is also contrary to the plain meaning of the MM definition in 1271.3(f)(1) and (2) which defines MM of cells separately from MM of structural tissue like adipose tissue.
An example is included to state specifically that isolating and removing stromal/stem cells from the underlying adipose tissue is MMM "because the processing breaks down and eliminates	Again, FDA artificially limits the plain meaning of its regulatory definition of MM in 1271.3(f)(1) and (2) unnecessarily. The definition intentionally separates the processing of cells in (2) from the	The relevant characteristics of adipose-derived stromal/stem cells is not to provide cushioning and support. That is the characteristic of the structural fat tissue as defined by 1271.3(f)(1) as MM

FDA Guidance Provision	Comment	Rationale
the structural components that provide cushioning and support, thereby altering the original relevant characteristics of the HCT/P relating to its utility for reconstruction, repair or replacement." (Example 10-1)	processing of their underlying structural tissue in (1). For the stromal/stem cells themselves, if "processing does not alter the[ir] relevant biological characteristics," then it is allowable as MM. Breaking down the relevant characteristics of the structural tissues in which these stem cells are located is not relevant to the "biological characteristics of these stem cells themselves when it is the cells which are the intended product, and not the fat tissue from which they are separated. Again the distinction here should be based on what is used to process and isolate the cells. If FDA approved reagents are used, the cells should be regulated under 1271/361. If non-FDA approved reagents are used, then the cells should be regulated under 351.	only if processing does not alter that structural tissues utility. This part of the MM definition only applies if it is tissue itself that is product (HCT/P). When isolating or removing stem cells, it is these cells that are the product, so (f)(2) and not (F)(1) apply. Since these stromal/stem cells possess biological characteristics that allow them to divide, multiply, expand and differentiate, processing the separated cells in this manner fits within the definition of MM and should be permitted.
In Section C of the Draft Guidance, FDA focuses on the cells themselves, and their relevant biological characteristics. It states that these characteristics include: differentiation and activation state, proliferation potential, and metabolic activity. Its examples again include stem cells. In the case of hematopoietic	The science in the field does not require FDA to take such a restrictive and narrow "either-or" approach. The relevant biological characteristics of cells include the ability to divide, expand and proliferate. However, the only example FDA provided in the draft guidance to illustrate allowable MM was separating	Stem cell therapy could be launched successfully in the U.S. by FDA interpreting its MM regulation according to its clear meaning as intended. Here, if cells maintain the internal biological mechanisms to proliferate or differentiate, allowing them to do so in a neutral laboratory medium would not

FDA Guidance Provision	Comment	Rationale
stem/progenitor cells, cell selection using a mobilized peripheral blood apheresis product to obtain a higher concentration of stem cells for transplantation to repopulate the bone marrow would be deemed MM, while incubating selected placental/umbilical cord blood products in a laboratory vessel containing culture media and growth factors to achieve a large number of cells capable of long-term repopulation of the bone marrow is MMM because the processing affects the production of intracellular or cell-surface proteins and other markers of cell lineage, activation state, and proliferation—thereby altering the cells' relevant biological characteristics of multipotency and capacity for self-renewal.	existing cells mechanically and using the stem cells already produced. Since cells contain the ability to reproduce and proliferate, allowing them to do so naturally in a supportive medium arguably does not alter their relevant biological characteristic to divide or proliferate.	create any safety risks if good laboratory and tissue practices are observed.

Attachment IV
Bipartisan Policy Center Comments
FDA Draft Guidance - Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception

FDA Guidance Provision	Comment	Rationale
Guidance intended to merely clarify application of §1271.15(b) which states simply that "[y]ou are not required to comply with the requirements of [Part 1271] if you are an establishment that removes HCT/Ps from an individual and implants such HCT/Ps into the same individual during the same surgical procedure."	This exception is already narrow requiring use of autologous cells within the same venue and surgical procedure. This provision is based entirely on the stated rationale that [t]he communicable disease risks, as well as the safety and efficacy risks, would generally be no different than those typically associated with surgery." (Guidance pg. 2)	The basis of 1271 and the same surgical procedure exception is exclusively an evaluation of the degree to which contamination under the standards set by §361 of the PHSA is prevented. If contamination is unlikely, the procedure should be allowed as it is for most surgical transplants.
The Guidance, not the regulation, creates an additional requirement using the words "such HCTP/s" in the regulation to mean that they remain in their original form. In a footnote (Footnote 4, Guidance pg. 3), this new term is explained as meaning of that new standard is not minimal manipulation with such processing steps typically causing the HCT/P to no longer be "such HCT/P." Rather the HCT/P can only be "rinsed, cleaned, sized or shaped."	There is nothing in a plain reading of the clear language of the regulation that limits the processing of the HCT/P to rinsing, cleaning, sizing and shaping. This standard was made up by FDA in this Guidance to limit the language of the regulation even more narrowly to use with tissue only and not cells. This language completely eliminates any use of the exception to permit cell therapy, even if the cells are autologous, minimally manipulated, used homologously, and are administered in the same surgical procedure.	Like the other guidances related to HCT/Ps, a principle objective of this guidance also appears to be preventing use of cell therapy or regenerative medicine under §1271. Rather than creating a new regulatory standard for the degree of processing permitted during the same surgical procedure, FDA should evaluate the likelihood of contamination under §361 and/or allow processing determined to be not more than minimally manipulated under §1271.3(f)(2).

FDA Guidance Provision	Comment	Rationale
	When liquid tissues (mobilized blood, cord blood, bone marrow) are used in the autologous or related allogeneic setting, processing to include separation of various cell population through density gradient separation (e.g. mononuclear cell enrichment, RBC depletion, Plasma depletion, cryopreservation and thawing with washing are allowed.	The minimal manipulation guidance should apply.
The examples used in this guidance of same surgical procedure include only transfer of tissues not cells (e.g., autologous skin grafting" and "coronary artery bypass surgery"). (Guidance pg. 4)	This exception should be applied to the narrow use of stem cells. Specific examples should be provided of stem cell uses.	Cell transplants should also be permitted to use this exception.