The Florida Senate

BILL ANALYSIS AND FISCAL IMPACT STATEMENT

(This document is based on the provisions contained in the legislation as of the latest date listed below.)

Prepared By: The Professional Staff of the Committee on Health Policy

BILL:	SB 1508
INTRODUCER:	Senator Young
SUBJECT:	Use of Stem Cells in a Clinic Setting
DATE:	February 5, 2018
REVISED:	

	ANALYST	STAFF DIRECTOR	REFERENCE	ACTION
1.	Rossitto-Van Winkle	Stovall	HP	**Favorable**
2.			AP	
3.			RC	
4.				

I. Summary:

SB 1508 creates a regulatory framework for the use of stem cells by doctors in a clinic setting. The bill provides definitions for clinic and stem cell and requires clinics to be registered, with certain exceptions. The Department of Health (DOH) must adopt rules for clinic registration and annual inspection. The Board of Medicine (BOM), and the Board of Osteopathic Medicine (BOOM) must adopt rules on advertising, adverse incident reporting, and informed consent.

Each stem cell clinic must have a designated physician who is responsible for complying with all the registration and operation requirements. The clinic must notify the DOH within 10 days following the termination of the designated physician and of the replacement designated physician. The bill gives the DOH authority to suspend a clinic's registration if the clinic fails to have a designated physician practicing at each clinic location. A physician is subject to discipline by his or her medical board if the physician practices in a clinic that is not registered. The bill gives the DOH disciplinary authority to impose fines on the physician or clinic for violating this section, the Florida Drug and Cosmetic Act, and certain provisions of the federal Food, Drug and Cosmetic Act (FDCA). In determining if a penalty is to be imposed, and the amount, the bill delineates specific factors the DOH must consider.

The effective date of the bill is July 1, 2018.

II. Present Situation:

Stem Cells

Stem cells are unspecialized cells that have the ability to divide for indefinite periods of time in culture median, and to give rise to specialized cells.[1] Stem cells have the potential to develop into

[1] National Institutes of Health, Stem Cell Information, Glossary, *Stem Cell* https://stemcells.nih.gov/glossary.htm#stemcells (last visited Feb. 4, 2018).

many different types of cells during early life and growth. In addition, in many tissues, stem cells serve as an internal repair system, dividing essentially without limit, to replenish other cells as long as the person is still alive. When a stem cell divides, each new cell has the potential to either remain an undifferentiated stem cell; or become a cell with a specialized function, such as a muscle, red blood, or brain cell.[2]

Stem cells are distinguished from other cells by two important characteristics:

- Stem cells are unspecialized cells capable of renewing themselves through cell division; and
- Stem cells can be induced to become tissue-specific or organ-specific cells, under certain physiologic or experimental conditions.[3]

In some organs, such as the alimentary canal (gut) and bone marrow, stem cells regularly divide to repair and replace worn out or damaged tissues. In other organs, such as the pancreas and the heart, stem cells only divide under special conditions.[4]

Until recently, scientists primarily worked with two kinds of stem cells from animals and humans: embryonic stem cells;[5] and non-embryonic "somatic" or "adult" stem cells.[6] Stem cells offer new potentials for treating diseases such as diabetes and heart disease, given their unique regenerative abilities. However, much work remains to be done in the laboratory and the clinic to understand how to use these cells for cell-based therapies to treat disease. This practice is referred to as regenerative or reparative medicine.[7]

Federal Regulation of Stem Cells

The U.S. Food and Drug Administration (FDA) has taken the position, under 21 C.F.R. 1271, that certain stem cells are to be labeled a *drug*, and subject to FDA regulation, depending on if the stem cell has been derived from structural tissue or non-structural tissue, in a manufacturing process involving more than minimal manipulation.[8]

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[2]National Institutes of Health, *Stem Cell Basics I.*, https://stemcells.nih.gov/info/basics/1.htm (last visited Jan. 10, 2018).
[3] *Id.*
[4] *Id.*
[5] Embryonic stem cells are primitive undifferentiated cells that are derived from preimplantation-stage embryos. They are capable of dividing without differentiating for a prolonged period in culture; and are known to develop into cells and tissues of the three primary germ layers. The three germ layers are the ectoderm, the mesoderm, and the endoderm. *See* National Institutes of Health, *Stem Cell Information, Glossary, Embryonic Stem Cells,* https://stemcells.nih.gov/glossary.htm#stemcells (last visited Jan. 10, 2018).
[6] Somatic (adult) stem cells are relatively rare undifferentiated cells found in many organs and differentiated tissues with a limited capacity for both self-renewal (in the laboratory) and differentiation. Such cells vary in their differentiation capacity, but it is usually limited to cell types in the organ of origin. *See* National Institutes of Health, *Stem Cell Information, Glossary, Somatic (adult) Stem Cells,* https://stemcells.nih.gov/glossary.htm#stemcells (last visited Jan. 10, 2018).
[7] National Institutes of Health, *Stem Cell Basics I.*, https://stemcells.nih.gov/info/basics/1.htm (last visited Jan. 10, 2018).
[8] U.S Department of Health and Human Services, Food and Drug Administration, Center for Evaluation and Research, Center for Devices and Radiological Health, Office of Combination Products, (Nov. 2017, corrected Dec. 2017), *Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use, Guidance for Industry and Food and Drug Administration Staff,* https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/cellularandgenetherapy/ucm585403.pdf (last visited Jan. 19, 2018). Section 1271.10(a)(1) provides that one of the criteria for an HCT/P to be regulated solely under s. 361 of the PHSA and the regulations in Part 1271, is that the HCT/P is only "minimally manipulated." As defined in 21 CFR 1271.3(f), "minimal manipulation" means: 1) For *structural tissue*, processing that *does*

The FDA defines a drug as an "article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles" (other than food) intended to affect the structure or function of the body."[9] Under this definition the FDA regulates articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion or transfer into a human recipient as "human cells, tissues, or cellular or tissue-based products (HCT/Ps)" which are stem cells.[10]

The U.S. Center for Biologics Evaluation and Research (CBER) regulates HCT/Ps.[11] Examples of HCT/Ps include, but are not limited to, bone, skin, corneas, ligaments, tendons, muscles, fat, dura mater, heart valves, hematopoietic stem/progenitor cells derived from peripheral and cord blood, oocytes and semen.[12] The CBER does not regulate the transplantation of vascularized human organ transplants such as kidney, liver, heart, lung or pancreas. The Health Resources Services Administration (HRSA) oversees the transplantation of vascularized human organs.[13]

Minimally manipulated bone marrow is also used in stem cell treatments, but not considered by the FDA regulations to be an HCT/Ps,[14] and thus not regulated by the FDA.[15] The Health Resources and Services Administration, an agency of the U.S. Department of Health and Human Services, regulates minimally manipulated bone marrow stem cells uses for transplant.[16]

Because of the unique nature of HCT/Ps, the FDA uses a tiered, risk-based approach to the regulation of HCT/Ps, rather than the Federal Food, Drug and Cosmetic Act (FDCA) for products that meet the definition of a drug, biologic or device.[17] The tiered, risk-based approach

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not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement (emphasis added); or 2) For *cells or nonstructural tissues*, processing *does not alter the relevant biological characteristics of cells or tissues*. Note: the FDA considers the processing of an HCT/P to be, "more than minimal manipulation," if information does not exist to show that the HCT/P qualifies for regulation solely under s. 361 of the PHSA. *See* 21 C.F.R. 1271.21 and 1271.10.

[9] 21 U.S C. s. 321(g).

[10] 21 C.F.R. 1271.3(d).

[11] See 21 C.F.R., 1270 and 1271. The CBER is a part of the Food and Drug Administration.

[12] The following are not considered HCT/Ps: (1) Vascularized human organs for transplantation; (2) Whole Blood or blood components or blood derivative products subject to listing under 21 C.F.R. ss. 607 and 207, respectively; (3) Secreted or extracted human products, such as milk, collagen, and cell factors, except that semen is considered an HCT/P; (4) Minimally manipulated bone marrow for homologous use and not combined with another article (except for water, crystalloids, or a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the bone marrow); (5) Ancillary products used in the manufacture of HCT/P; (6) Cells, tissues, and organs derived from animals other than humans; (7) In vitro diagnostic products as defined in 21 C.F.R. s. 809.3(a); and (8) Blood vessels recovered with an organ, as defined in 42 C.F.R. s. 121.2 that are intended for use in organ transplantation and labeled "For use in organ transplantation only." *See also* 21 C.F.R. 1271.3(d).

[13] U.S. Food and Drug Administration, *Tissue and Tissue Products, available at* https://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/default.htm (last visited Jan. 10, 2018).

[14] *See* 21 C.F.R. 1271.3(d)(4).

[15] U.S. Food and Drug Administration, Food and Drug Administration, *FDA Warms About Stem Cell Therapies*, https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm286155.htm (last visited Jan. 17, 2018).

[16] U.S. Department of health and Human Services, Health Resources and Services Administration, *Healthcare Systems, available at* https://www.hrsa.gov/sites/default/files/ourstories/organdonation/factsheet.pdf (last visited Jan. 19, 2018).

[17] Although the FDA is authorized to apply the requirements in the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act to those products that meet the definition of drug, biologic, or device, under this tiered, risk-based approach, those HCT/Ps that meet specific criteria or fall within detailed exceptions do not require premarket review or approval. *See* U.S Department of Health and Human Services, Food and Drug Administration, Center for Evaluation and

includes how the transmission of communicable diseases can be prevented; what process controls are necessary to prevent contamination and preserve the integrity and function of the products; and how the clinical safety and effectiveness can be assured.[18]

The tiered, risk-based approach is contained in regulations referred to as the "tissue rules," issued by the FDA, under the communicable disease authority of s. 361 of the Public Health Service Act (PHSA).[19]

For an HCT/P to be regulated solely under the requirements of s. 361 of the PHSA, and 21 C.F.R. 1271, it must meet all of the following criteria:[20]

- The HCT/P is *minimally manipulated*;[21]
- The HCT/P is intended for homologous use only;[22]
- The HCT/P is not combined with any other article, except water, crystalloids, or a sterilizing, preserving, or storage agent; and
- Either:
  - The HCT/P does not have a systemic effect, and is not dependent upon the metabolic activity of living cells, for its primary function; or
  - The HCT/P has a systemic effect, or is dependent upon the metabolic activity of living cells for its primary function, and:
    - Is for autologous use;[23]
    - Is for allogeneic use;[24] or

Research, Center for Devices and Radiological Health, Office of Combination Products, Nov. 2017, corrected Dec. 2017, *Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use, Guidance for Industry and Food and Drug Administration Staff*, https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/cellularandgenetherapy/ucm585403.pdf (last visited Jan. 19, 2018).

[18] *Id.*

[19] 42 U.S.C. s. 264.

[20] 21 C.F.R. 1271.10.

[21] 21 C.F.R. 1271.10(a)(1) provides that one of the criteria for an HCT/P to be regulated solely under s. 361 of the PHSA and the regulations in 1271, is that the HCT/P is only "minimally manipulated". As defined in 21 C.F.R. 1271.3(f), "minimal manipulation" means: 1) For *structural tissue*, processing that *does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement* (emphasis added); or 2) For *cells or nonstructural tissues*, processing *does not alter the relevant biological characteristics of cells or tissues*. Note: the FDA considers the processing of an HCT/P to be, "more than minimal manipulation," if information does not exist to show that the HCT/P qualifies for regulation solely under s. 361 of the PHSA.

[22] 21 C.F.R. 1271.10(a)(2), provides that one of the criteria for an HCT/P to be regulated solely under s. 361 of the PHSA, and the regulations in 1271, is that the "HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent." As defined in 21 C.F.R. 1271.3(c), "homologous use" means the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor. This criterion reflects the FDA's conclusion that there would be increased safety and effectiveness concerns for HCT/Ps that are intended for a non-homologous use, because there is less basis on which to predict the product's behavior. *See supra* note 8, at 4.

[23] *"Autologous use"* means the implantation, transplantation, infusion, or transfer of human cells or tissue back into the individual from whom the cells or tissue were recovered. *See* 21 C.F.R. 1271.3(a).

[24] *"Allogeneic use"* means taken from different individuals of the same species. Two or more individuals are said to be allogeneic to one another when the genes at one or more loci are not identical. Medicinenet.com, *Medical Definition of Allogeneic*, https://www.medicinenet.com/script/main/art.asp?articlekey=25266 (last visited Jan. 10, 2018).

- Is for reproductive use.[25]

To apply the minimally manipulated criteria, the FDA first determines if the HCT/P to be transplanted was derived from structural tissue or cellular/nonstructural tissue. This determination is made based on the characteristics of the HCT/P in the donor, before recovery, and before any processing takes place.[26]

In applying the minimally manipulated analysis the FDA acknowledges that HCT/Ps perform multiple functions; and that structural tissues contain cells. The FDA also acknowledges that some manufacturers assert that an HCT/P has both a structural and cellular/nonstructural function. However, under FDA regulations, HCT/Ps are considered either structural tissues or cells/nonstructural tissues. HCT/Ps that physically support or serve as a barrier or conduit, or connect, cover, or cushion are generally considered structural tissues for the purpose of applying the HCT/P regulatory framework. The FDA gives the following examples of what it considers structural tissue:

- Bone;
- Skin;
- Amniotic membrane and umbilical cord;
- Blood vessel;
- Adipose tissue;
- Articular cartilage;
- Non-articular cartilage; and
- Tendon or ligament.[27]

HCT/Ps that serve metabolic or other biochemical roles in the body such as hematopoietic, immune, and endocrine functions, are generally considered cells/nonstructural tissues for the purpose of applying the FDA HCT/P regulatory framework. The FDA examples of cells or nonstructural tissues include:

- Reproductive cells or tissues (oocytes);
- Hematopoietic stem/progenitor cells (cord blood);
- Lymph nodes and thymus;
- Parathyroid glands;
- Peripheral nerve; and
- Pancreatic tissue.[28]

The FDA defines processing as any activity performed on an HCT/P, other than:

- Rinsing;
- Cleaning;
- Recovery;
- Donor screening;

[25] 21 C.F.R. 1271.10(a).
[26] *Supra* note 8.
[27] *Id.*
[28] *Supra* note 8.

- Donor testing;
- Storage;
- Sizing;
- Labeling;
- Packaging;
- Distribution;
- Testing for microorganisms;
- Preparation;
- Sterilizations;
- Steps to inactivate or remove adventitious agents;
- Preservation for storage; and
- Removal from storage.[29]

Under this definition, processing includes:

- Cutting;
- Grinding;
- Shaping;
- Culturing;
- Enzymatic digestion; and
- Decellularization.[30]

An HCT/P is exempt from registration and regulation under the PHSA, and 21 C.F.R. 1271, if the establishment:[31]

- Uses the HTC/P's solely for nonclinical scientific or educational purposes;
- Removes HCT/P's from an individual, and implants such HCT/P's into the same individual, during the same surgical procedure;
- Is a carrier who accepts, receives, carries, or delivers HCT/P's in the usual course of business;
- Does not recover, screen, test, process, label, package, or distribute, but only receives or stores HCT/P's, solely for implantation, transplantation, infusion, or transfer within your facility;
- Only recovers reproductive cells or tissue and immediately transfers them into a sexually intimate partner of the cell or tissue donor; or
- If you are an individual under contract with a registered establishment, and engaged solely in recovering cells or tissues and sending the recovered cells or tissues to the registered establishment, you are not required to register or list your HCT/P's independently, but you must comply with all other applicable requirements. [32]

[29] See 21 C.F.R. 1271.3(ff).
[30] *Supra* note 8.
[31] Establishment means a place of business under one management, at one general physical location, that engages in the manufacture of human cells, tissues, and cellular and tissue-based products. Establishment includes: (1) Any individual, partnership, corporation, association, or other legal entity engaged in the manufacture of human cells, tissues, and cellular and tissue-based products; and (2) Facilities that engage in contract manufacturing services for a manufacturer of human cells, tissues, and cellular and tissue-based products. 21 C.F.R. 1271.3(b).
[32] 21 C.F.R. 1271.15.

If an HCT/P does not meet the above criteria, and the manufacturer of the HCT/P does not qualify for an exception,[33] the HCT/P will be regulated as a drug, device, and/or biological product under the FDCA, the PHSA,[34] and applicable regulations;[35] and premarket review will be required.[36]

According to the FDA, if a manufacturer/establishment isolates cells from structural tissue to produce a cellular therapy product, the definition of minimal manipulation applies, regardless of the method used to isolate the cells. This is because the assessment of whether the HCT/P is a structural tissue or cellular/nonstructural tissue is based on the characteristics of the HCT/P as it exists in the donor, prior to recovery, and prior to any processing that takes place.[37]

The federal law requires tissue establishments[38] that do not meet an exemption, to:
- Screen and test donors;
- Prepare and follow written procedures for the prevention of the spread of communicable disease; and
- Maintain records.[39]

The FDA has published rules to broaden the scope of products subject to regulation, and to include more comprehensive requirements, to prevent the introduction, transmission and spread of communicable disease. Those rules include requiring the tissue establishments to:
- Register and submit a list to the FDA of every HCTP it manufactures within five days after operations begin, or within 30 days of the effective date of the registration;[40]
- Determine donor eligibility, including screening and testing;[41] and
- To recover, process, store, label, package, and distribute HCT/Ps, and screen and test cell and tissue donors, in such a way that prevents the introduction, transmission, or spread of communicable diseases.[42]

The requirements are intended to improve protection of the public health while minimizing regulatory burden.[43]

The only HCT/Ps that are FDA-approved for use in the United States consist of blood-forming stem cells (hematopoietic progenitor cells) derived from cord blood. These products are approved for limited use in patients with disorders that affect the body system that is involved in

[33] 21 C.F.R., 1271.10, 1271.15 and 1271.155.
[34] 42 U.S.C. s. 262.
[35] 21 C.F.R.1271.
[36] *Supra* note 8.
[37] *Id.*
[38] *Supra* note 31.
[39] *See* 21 C.F.R 1270 and 1271.2121.
[40] 21 C.F.R. 1271.21.
[41] 21 C.F.R. 1271.45.
[42] *Id.*
[43] U.S. Department of Health and Human Services, Food and Drug Administration, *Tissue and Tissue Products*, https://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/default.htm (last visited Jan. 10, 2018).

the production of blood (called the "hematopoietic" system). The FDA-approved stem cell products are listed on the FDA website.[44]

Stem Cells from Adipose Tissue

Structural HCT/Ps include cells obtained from adipose tissue. Adipose tissue is typically defined as a connective tissue that stores energy in the form of lipids, insulates the body, and provides cushioning and support for subcutaneous tissues and internal organs. It is composed of clusters of cells (adipocytes) surrounded by a reticular fiber network and interspersed small blood vessels, divided into lobes and lobules by connective tissue septa.[45] Additionally, adipose tissue contains other cells, including pre-adipocytes, fibroblasts, vascular endothelial cells, and a variety of immune cells.[46]

The FDA, by way of example, specifically addresses the original relevant characteristics of adipose tissue relating to its utility to provide cushioning and support, which includes its bulk and lipid storage capacity. A manufacturer that recovers adipose tissue by tumescent liposuction and processes (e.g., enzymatically digests, mechanically disrupts, etc.) the adipose tissue to isolate cellular components (with or without subsequent cell culture or expansion), to stromal vascular fraction (SVF), is considered by the FDA to be more than minimally manipulating the HCT/P. This is because the processing breaks down and eliminates the adipocytes and the surrounding 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.[47]

The FDA treats the recovery of adipose tissue from a donor for allogenic or autologous use, the recovery of a structural tissue. If the adipose tissue is then processed through enzymatic digestion, mechanical disruption etc., to isolate non-adipocyte, or non-structural components, from the adipose tissue (with or without subsequent cell culture or expansion), the processing of the structural tissues becomes stromal vascular fraction (SVF), and is considered more than minimally manipulated.[48] If the SVF is then administered intravenously or intrathecally, to a recipient to treat a variety of diseases or conditions, it will not be solely regulated the PHSA.[49]

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[44] U.S. Department of Health and Human Services, Food and Drug Administration, *Approved Cellular and Gene Therapy Products*, (page last updated Feb. 2, 2018) *available at* https://www.fda.gov/biologicsbloodvaccines/cellulargenetherapyproducts/approvedproducts/default.htm (last visited Jan. 18, 2018).

[45] Some HCT/Ps from adipose tissue may also be regulated as devices. For more information about device regulation, See *CDRH's webpage Device Advice – Overview of Medical Device Regulation*, (page last updated Aug. 14, 2015) *available at* http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/default.htm (last visited Jan.10, 2018).

[46] Brown SA, Levi, B, Lequeux, C, et al. Plastic Reconstructive Surgery, *Basic Science Review on Adipose Tissue for Clinicians*, 126:1936, 2010.

[47] *Supra* note 8.

[48] This is because the connective tissue and structural components of the adipose tissue are entirely removed from the non-adipocyte or non-structural isolates, and thus altering the original relevant characteristics relating to the tissues utility for reconstruction, repair, and replacement. *See supra* note 8 and 21 C.F.R. 1271.3(f)(1).

[49] 42 U.S.C. 264 and s. 301 PHSA.

Florida Regulation of Stem Cells

Stem Cell Preparation/Manufacturing

The Department of Business and Professional Regulation (DBPR) administers and enforces the Florida Drug and Cosmetic Act (FDCA) to prevent fraud, adulteration, misbranding, or false advertising in the preparation, manufacture, repackaging, or distribution of drugs, devices, and cosmetics.[50] In Florida, "a person may not sell, offer for sale, hold for sale, manufacture, repackage, distribute, or give away any new drug unless an approved application has become effective under the federal act or unless otherwise permitted by the Secretary of the United States Department of Health and Human Services for shipment in interstate commerce."[51]

The FDCA defines a "drug" as an article that is:

- Recognized in the current edition of the United States Pharmacopoeia and National Formulary (USP-FM),[52] official Homeopathic Pharmacopoeia of the United States (HPUS),[53] or any supplement to any of those publications;
- Intended for use in the diagnosis, cure, mitigation, treatment, therapy, or prevention of disease in humans or other animals;
- Intended to affect the structure or any function of the body of humans or other animals; or
- Intended for use as a component of any article specified in paragraph (a), paragraph (b), or paragraph (c), and includes active pharmaceutical ingredients,[54] but does not include devices or their nondrug components, parts, or accessories.[55]

The FDCA defines the manufacturing of a drug to mean the preparation, deriving, compounding, propagation, processing, producing, or fabrication of a substance into a drug.[56] Under the Act a manufacturer of a drug is a person, co-licensed partner, or affiliate, of a person who holds a New Drug Application, an Abbreviated New Drug Application, a Biologics License Application, or a New Animal Drug Application approved or licensed under the federal Public Health Service Act[57] for such drug or biologics, or if such drug or biologics are not the subject of an approved application or license, the person who manufactured the drug or biologics.

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[50] *See* part I of ch. 499, F.S.
[51] Section 499.023, F.S.
[52] USP-NF is a combination of two compendia, the United States Pharmacopeia (USP) and the National Formulary (NF). It contains standards for medicines, dosage forms, drug substances, excipients, biologics, compounded preparations, medical devices, dietary supplements, and other therapeutics. *See* 21 U.S.C. s. 301(g)(1).
[53] The HPUS is declared a legal source of information on drug products (along with the USP/NF) in the Federal Food Drug and Cosmetic Act, 21 U.S.C. § 301. Section 201(g)(1) of the Act. 21 U.S.C. s. 321 defines the term "drug" as articles recognized in the official United States Pharmacopoeia, official Homœopathic Pharmacopœia of the United States, or official National Formulary or any supplement to any of them.
[54] Section 499.003(1), F.S., defines an "active pharmaceutical ingredient" includes any substance or mixture of substances intended, represented, or labeled for use in drug manufacturing that furnishes or is intended to furnish, in a finished dosage form, any pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, therapy, or prevention of disease in humans or other animals, or to affect the structure or any function of the body of humans or animals.
[55] Section 499.003(18), F.S.
[56] Section 499.003(28), F.S.
[57] 42 U.S.C. s. 262.

Stem cells recovered, processed, and implanted in Florida that fit the above definitions, are "unapproved new drugs" under both federal and state regulation; and require a manufacturing permit issued by the DBPR to ensure that the drugs are manufactured in accordance with good manufacturing practices.[58]

Stem Cell Implantation or Transplantation

Stem cells may be collected, processed, and implanted or transplanted in a physician's office, health care clinic, ambulatory surgical center, or a hospital.

Physician's Office

The DOH Office of Surgery Registration and Inspection Program, was established to register and set standards for allopathic and osteopathic physicians performing surgery in an office setting. The DOH requires all physicians who perform the following to register their office with the DOH:

- Liposuction procedures where more than 1,000 cubic centimeters of supernatant fat is removed;
- Level II procedures lasting more than five minutes; and
- All Level III surgical procedures.[59]

The DOH will inspect those registered, that are not nationally accredited, to ensure the safety of the people of Florida.[60]

Under current regulations, it is unclear whether stem cell implantation or transplantation in physicians' offices is subject to inspection and regulation by the DOH. Hypothetically, if the physician performs a procedure by removing less than 4000 cc of supernatant fat, uses no sedation, and the procedure lasts less than five minutes, it is not subject to the DOH regulation.[61]

Health Care Clinics

The Health Care Clinic Act,[62] provides the Agency for Health Care Administration (AHCA) with licensing and regulatory authority to provide standards and oversite for health care clinics.[63] A clinic is defined as an entity where health care services are provided and which tenders charges for reimbursement for such services. Numerous exceptions to licensure exist.[64]

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[58] Department of Business and Professional Regulation, Division of Drugs, Devices and Cosmetics, *Does my company need a permit? available at* http://www.myfloridalicense.com/dbpr/ddc/ProgramFAQ1.html (last visited Jan. 18, 2018). See also ss. 458.309(3) and 458.351, F.S.; Rule 64B8-9.009, F.A.C.

[59] Department of Business and Professional Regulation, Division of Drugs, Devices and Cosmetics, *Does my company need a permit? available at* http://www.myfloridalicense.com/dbpr/ddc/ProgramFAQ1.html (last visited Jan. 18, 2018). See also ss. 458.309(3) and 458.351, F.S.; Rule 64B8-9.009, F.A.C.

[60] The Department of Health, Licensing and Regulation, *Office Surgery Registration,* http://www.floridahealth.gov/licensing-and-regulation/office-surgery-registration/index.html (last visited Jan. 22, 2018).

[61] See Rule 64B8-9.9009, F.A.C.

[62] Part X of ch. 400, F.S.

[63] Section 400.990, F.S.

[64] Section 400.9905(4). F.S.

The AHCA interprets this phrase to solely include entities that bill third parties, such as Medicare, Medicaid, and insurance companies. Entities that provide health care services and accept "cash only" for services are excluded from the definition of "clinic" and are not subject to licensure or regulation by the AHCA.[65]

Hospitals and Ambulatory Surgical Centers

The AHCA is responsible for licensing, registering, and regulating hospitals and Ambulatory Surgical Centers (ASC) pursuant to ch. 395, F.S.[66]

An ASC is a facility, not a part of a hospital, that has as its primary purpose to provide elective surgical care, in which the patient is admitted and discharged in the same working day, and is not permitted to stay overnight.

Regulation of Physicians in Florida

The BOM and the BOOM (the boards), within the DOH, have the authority to adopt rules to regulate the practice of medicine and osteopathic medicine, respectively. The boards have authority to establish, by rule, standards of practice and standards of care for particular settings.[67] Such standards may include education and training, medications including anesthetics, assistance of and delegation to other personnel, sterilization, performance of complex or multiple procedures, records, informed consent, and policy and procedures manuals.[68]

Currently the BOM is warning physicians and consumers that they should be aware of the risks involved in stem cell therapies and regenerative medicine that have not been FDA approved.[69] The BOM warns physicians providing stem cell treatment that he or she should have an investigational new drug application (IND) or a single patient IND for Compassionate or Emergency Use.[70] Florida does not specifically regulate clinics that perform treatments using stem cells; but the Boards have authority to investigate and discipline physicians who fail to meet the standard of care for providing any medical services. In 2013, the Board of Medicine revoked the licenses of two physicians in administrative cases involving stem cells for failing to meet the standard of care.[71]

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[65] Agency for Health Care Administration, *Ambulatory Surgical Centers* http://ahca.myflorida.com/MCHQ/Health_Facility_Regulation/Hospital_Outpatient/ambulatory.shtml (last visited Feb. 1, 2018).
[66] Section 395.002(3), F.S.
[67] Sections 458.331(v) and 459.015(z), F.S.
[68] *Id*.
[69] The Department of Health, Board of Medicine, *Information on Stem Cell Clinics Offering Unapproved Therapies*, http://flboardofmedicine.gov/latest-news/october-2015-newsletter/ (last visited Jan. 31 2018).
[70] *Id*.
[71] Department of Health, *Senate Bill 1508 Analysis* (Jan. 11, 2018) (on file with the Senate Committee on Health Policy).

III. Effect of Proposed Changes:

Stem Cell Clinic Registration and Regulation

The bill requires a clinic or physician who advertises, uses, or purports to use stem cells or products containing stems cells to register with the DOH.

The bill defines a clinic as a privately or publicly owned facility or office that:

- Advertises a service that uses, or purports to use, stem cells or a product containing stem cells to diagnose, cure, mitigate, treat, provide therapy for, or prevent an injury or disease; or
- Performs any procedure that is intended to diagnose, cure, mitigate, treat, provide therapy for, or prevent an injury or disease that uses, or purports to use, stem cells or a product containing stem cells which has not been approved by, or is not the subject of a clinical trial approved of by the FDA.

The bill defines a stem cell as allogenic or autologous cell that has been altered or processed to become undifferentiated, losing its original structural function, so that it can become differentiated into a specialized cell type. The definition excludes cells that are only rinsed, cleaned, or sized and remain differentiated. A clinic does not have to register with the DOH if it:

- Is licensed under ch. 395, F.S.;[72]
- Is wholly owned and operated by one or more Florida-licensed physicians;
- Is affiliated with an accredited medical school that provides training to medical students, residents, or fellows; or
- Solely performs one or more of the following:
  - Collection of umbilical cord blood cells for blood banking;
  - Collection, transfer, or insemination of oocytes; or
  - Injection or infusion of platelet-rich plasma.

Each clinic must be registered separately. A clinic or physician must submit a new registration if there is a change of ownership. The bill requires each clinic to designate a physician who holds a full, active and unencumbered Florida license to be responsible for compliance with clinic registration and operation requirements.

A clinic must notify the DOH within ten days of a change in the designated physician. If a clinic fails to have a designated physician, the DOH may issue an emergency suspension[73] of the clinic's registration.

The bill authorizes the DOH to impose a fine of up to $5,000 per violation if the clinic fails to comply with the registration requirement, the DOH and Board rules, the Florida Drug and Cosmetic Act,[74] or the federal Food, Drug, and Cosmetic Act.[75] When determining if a fine should be imposed, and the amount of the fine, the DOH must consider:

[72] Chapter 395, F.S., governs the licensure and regulation of hospitals and surgery centers.
[73] The DOH may issue an emergency suspension, restriction, or limitation of a license if it finds that an immediate serious danger to the public health, safety, welfare exists.
[74] Chapter 499, F.S.
[75] 21 U.S.C. ss. 301 and 25, Stat. 1040 et seq.

- The gravity of the violation, including the existence and severity of patient deception, serious or physical mental harm, or the potential of such deception or harm;
- The actions taken by the physician, clinic, or designated physician to correct the violation;
- Whether there were previous violations at the clinic; and
- The financial benefits derived by the physician, clinic, or designated physician from committing or continuing to commit the violation.

If the physician, clinic, or designated physician fails to cease the violating behavior as of the date required by the DOH, each day the violation continues constitutes an additional, separate, and distinct violation. The DOH may impose a fine if the designated physician knowingly misrepresents that action had been taken to correct a violation. However, if it is an owner-operated clinic, the DOH may impose a fine and revoke or deny a clinic registration.

The bill requires the DOH to adopt rules for the implementation of the registration requirement, as well as an annual inspection of registered clinics. All costs for the registration and inspections must be borne by the clinic. The Boards must adopt rules regarding advertising, adverse incident reporting, and informed consent guidelines for the use, or purported use, of stem cells or products containing stem cells in a clinic required to register.

Physician Responsibilities

The bill requires a physician who performs a procedure using or purporting to use stem cells or products containing stem cells to follow the applicable good manufacturing practices for collecting, removing, processing, implanting, and transferring stem cells or products containing stems cells, pursuant to the federal Food, Drug, and Cosmetic Act[76] and federal law governing human cells, tissues, and cellular and tissue-based products.[77]

A physician who practices at a clinic that is not registered as required may be disciplined by his or her Board.

The bill provides an effective date of July 1, 2018.

IV. Constitutional Issues:

A. Municipality/County Mandates Restrictions:

None.

B. Public Records/Open Meetings Issues:

None.

[76] 21 U.S.C. ss. 301, et seq., and 52 Stat. 1040 et seq.
[77] 21 C.F.R. s. 1271.

C. Trust Funds Restrictions:

None.

V. Fiscal Impact Statement:

A. Tax/Fee Issues:

The DOH will experience an increase in revenue associated with the registration and inspections of clinics that use stem cells. SB 1508 provides that the person or entity that wants to register and operate a clinic must pay all cost for registration and inspection. The DOH estimates approximately 20 clinics would register initially.

B. Private Sector Impact:

None.

C. Government Sector Impact:

The DOH will experience a recurring increase in costs and workload associated with the registration, regulation, and inspections for clinics that use stem cells. Current budget authority is adequate to absorb this impact.

VI. Technical Deficiencies:

None.

VII. Related Issues:

None.

VIII. Statutes Affected:

This bill creates the following sections of the Florida Statutes: 458.352, 459.027.

IX. Additional Information:

A. Committee Substitute – Statement of Changes:
(Summarizing differences between the Committee Substitute and the prior version of the bill.)

None.

B. Amendments:

None.