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Arguments for a Different Regulatory Categorization and Framework for Stromal Vascular Fraction

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Although adipose tissue and cells show considerable promise for clinical translation in the emerging field of regenerative medicine, they present a challenge to the regulatory community both nationally and internationally. This commentary evaluates the status of adipose-derived therapeutics and considers regulatory approaches designed to maximize patient safety while advancing clinical translation in accordance with evidence-based medical science.

Keywords: cell therapy, regenerative medicine, adipose-derived stromal/stem cells, stromal vascular fraction cells, regulation

THE RAPIDLY EVOLVING field of regenerative medicine continues to grapple with challenges surrounding the promise and limitations of mesenchymal stem cells (MSCs) such as adipose-derived cells known as adipose-derived stromal/stem cells (ASCs) as well as stromal vascular fraction (SVF) cells. The clinical landscape of stem cell clinics has been characterized as medicine's ''wild west'' [1,2]. Recently, there have been highly publicized adverse events associated with adipose cell therapy, most notably blindness that developed in three patients receiving autologous SVF cells for age-related macular degeneration [3]. Unquestionably, such incidents require a greater level of accountability and enforcement among medical professionals. We share the Food and Drug Administration's (FDA's) concern with the present state of affairs and take this opportunity to offer a path forward ensuring patient safety that includes evidence-based medical practice.

In this article, we propose a way forward that protects patients within the confines of evidence-based medicine yet allows bringing adipose-based regenerative therapies to market in a more efficient way. The elements of this strategy are as follows. First, a modification of the risk tier to reflect a better understanding of the various risk profiles associated with different adipose-derived regenerative therapies. Second, keeping the ''rogue clinics'' out and ensuring patient protection by accreditation of regenerative therapy facilities and physicians so that no therapy is delivered unless by a fully accredited physician in an accredited facility. This model has worked well for the blood bank industry and surgicenters. Third, develop a national registry of regenerative therapies to track results and serve as a knowledge base for new insights and future directions. Fourth, integrate state medical societies and specialty boards into the process of shaping and enforcing adipose-based regenerative therapy policies.

Unfortunately, the discussions regarding adipose-derived cell therapies have fallen into a maelstrom of controversy. One must first recognize that although ASCs and SVF are both adipose derived they have different cell types, activities, and manufacturing processes.

- SVF [4] is a heterogeneous collection of cells isolated from lipoaspirate by mechanical or enzymatic means. Thus, although some cells are hematopoietic lineage cells (stem and progenitor cells <0.1%, granulocytes 10%–15%, monocytes 10%–15%, and lymphocytes 10%–15%) other subpopulations include endothelial cells 10%–15%, pericytes 3%–5%, and stromal cells 15%–30%. Some of these cells are cell lineage precursors, others are concerned with immune reactivity and modulation, and yet others with vascular homeostasis.

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- ASC [4,5] is a more narrowly defined subpopulation cells obtained after several passages in cell culture. The cells must express a specific set of cell markers ($CD105^+$, $CD73^+$, and $CD90^+$) and lack expression of others ($CD45^-$, $CD34^-$, $CD14^-$, and HLA-DR) surface molecules. These ASCs are multipotential and must have the ability to differentiate into osteoblasts, adipocytes, and chondroblasts.

Consequently, these very different cell preparations (one a freshly harvested heterogeneous population of cells and the other a cultured homogenous product) whose cell populations vary markedly in cell function and differentiation potential are best addressed distinctly (Table 1). Second, one must differentiate the risk profile of autologous versus allogeneic adipose-derived cell therapies. Finally, one must address the role of the physician and facility delivering the therapy (''rogue cells or rogue physicians?'').

Discussions about adipose-derived cell therapies benchmark the science and use of ASC and SVF cells relative to the knowledge base involving hematopoietic stem and progenitor cells (HSPCs). Although the body of peer-reviewed literature regarding ASC and SVF cells only began to emerge after a landmark basic science publication in 2001 [6], research involving HSPC dates back to the late 1940s and the large-scale radiation exposure of civilian populations at Hiroshima and Nagasaki. Within a decade, anecdotal reports appeared in the peer-reviewed clinical literature reporting uncontrolled (ie, anecdotal case report) patient outcomes [7]. The speed in HSPC clinical translation presumably reflected the severity and lethality of the underlying pathology as well as the desperation and limited options of patients, their families, and health care providers. Since then, the field has witnessed ongoing refinements in HSPC therapies as reflected in an ever-increasing body of scientific and clinical translational publications.

Unfortunately, along with the rise in publications regarding ASC and SVF therapies there has also been a proliferation of clinics offering as-yet unproven ASC and SVF therapies. These clinics cater to the desperation of hopeless patients with the promise of ''stem cell therapy.'' The FDA understandably is concerned with the ''wild west'' atmosphere within a clinical stem cell landscape in which treatments are offered by independent practitioners advertising unsubstantiated claims of efficacy with apparently little regulatory oversight. Clinics may even post a disclaimer on websites stating that the treatments are unapproved and ''at your own risk.'' Moreover, such treatments may be offered under a veil of research with the therapy being ''patient funded.'' The National Library of Medicine (www.clinicaltrials HYPERLINK ''www.clinicaltrials.gov'' HYPERLINK ''www .clinicaltrials.gov'' HYPERLINK ''www.clinicaltrials.gov/'' .gov) website is freely open for posting by entities across the globe, giving a potentially false appearance of credibility.

Because of the relative ease of preparation of SVF and the perception that the status of SVF in the regulatory risk tier (ie, human cell tissue/product [HCT/P] 361 vs. 351) is unclear, the most significant growth in clinics has been that of clinics providing unproven or untested SVF therapies. This combustible mix of unmet medical needs, an ambiguous regulatory pathway, untested therapies, and clinics rapidly rushing in to fill a void exploded into the national scene with the troubling publication of three cases of blindness after treatment of macular degeneration by SVF injection [3]. Behind the scenes, however, parties with greater compliance-oriented perspectives have been trying with varying degrees of success to grapple with this complex problem.

In an effort to control the growth of these clinics providing untested and unproven therapies the FDA has made an effort to clarify the ambiguities in the regulatory framework by issuing a set of guidance regarding stem cell therapies. The regulatory framework for human-based cellular and tissue-based therapies is the 21 CFR (Code of Federal Regulations) 1271, Human Cells, Tissues, and Cellular and Tissue-Based Products. It provides a risk-tiered classification of therapies as belonging to the HCT/P 361 or HCT/P 351. An HCT/P 361 does not need premarket approval, so it can have a direct and speedy pathway to the clinical setting. An HCT/P 351 requires premarket approval since it is regulated as a drug, device, and/or biological product. This is a costly and lengthy process that requires an investigational new drug (IND) application culminating in a biologics license application (BLA).

To be considered a lower risk HCT/P 361 [21 CFR 1271.10 (a)] that does not need premarket approval, the ''product'' must be (a) minimally manipulated, and (b) for homologous use only, and (c) does not combine the cells or tissues with another article. Under the regulation, the product either does not have a systemic effect or is not dependent upon the metabolic activity of living cells for its primary function (''structural tissue'') or it has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function (''nonstructural tissue'').

In the case of ASCs the risk tier designation is clear since it is a homogeneous culture of multipotential cells that have

Table 1. Present Regulatory Scheme—A Freshly Harvested Heterogeneous Group of Cells (Stromal Vascular Fraction) that Is used as an Autologous Product in a Same Day Surgery Setting Is Placed in the Same Risk Tier as Ex Vivo Cultured Cells Whose Origin can be Autologous or Allogeneic

	Adipose fragment ie, ''Fat Graft''	*SVF*	*Cultured ASCs autologous*	*Cultured ASCs, allogeneic*	*Physician, facility*
HCT/P 361	(''structural'' use)				Unregulated
HCT/P 351	(''metabolic'' use)	X	X	X	Unregulated

The risk assignment of SVF is based purely on an interpretation of 21 CFR 1271.3 (c) by the FDA that adipose tissue is predominantly of structural nature, whereas SVF mode of action is metabolic.

ASC, adipose-derived stromal/stem cell; FDA, Food and Drug Administration; HCT/P, human cell tissue/product; SVF, stromal vascular fraction.

been ''more than minimally'' manipulated, and is produced by combining cells and tissues with other articles to enable and facilitate the culturing of cells.

Unfortunately, the recent designation of SVF as a 351 tissue is based on a guidance document stating that ''for the purpose of applying the HCT/P regulatory framework,'' adipose is a structural tissue. This assertion seems to be contradicted by the regulations themselves, science and by the FDA's own cited sources.

21 CFR 1271.3 (c), regarding the homologous use states that the donor tissue (adipose tissue before harvest) may have a basic function or function*s* (structural or nonstructural), but 21 CFR 1271.10 (a) requires the product (processed adipose tissue into recipient) to be either structural or nonstructural. Thus, one can envisage a single adipose donor tissue specimen yielding a structural product (fat graft) for homologous use as structural support, and a cellular (SVF) product for homologous cellular use. The FDA assertion that adipose is a structural tissue artificially and arbitrarily imposes the product characteristics (being either structural or nonstructural) onto the donor tissue characteristics (having basic function or function*s*, ie, structural and nonstructural). The guidance thus apparently contradicts and potentially abrogates the regulation [21 CFR 1271.3 (c)].

The assertion that adipose tissue is primarily or predominantly structural also goes against current science. There is a substantial body of preclinical evidence supporting the innate endocrinological and immunological functions of adipose-derived cells in situ. A review of the literature between 2012 and 2017 identified 1 meta-analysis, 2 randomized controlled clinical trials and 16 case series, involving a total of 844 human subjects, using either ASC or SVF cells for what would be considered nonhomologous therapeutic purposes under FDA 21 CFR 1271 regulations [8]. The quantity and quality of this highly reproducible and growing body of evidence from independent international laboratories should not be lightly dismissed.

Finally, the FDA's cited authority for designating adipose tissue as structural is Junqueira's *Basic Histology: Text & Atlas, 13e Ch 5*. It cites clearly and emphatically that adipose tissue is connective tissue whose defining function is metabolic and nonstructural, coexisting with structural features. Thus, it is puzzling for the FDA guidance to use a source that contradicts this definition explicitly. Although the FDA's stance to control the growth of rogue clinics resulting in medical tragedies is fully understandable and merits support, we believe it is not optimally promoted at the expense of logic, science, and regulatory integrity.

Regardless, both ASC and SVF therapies are presently placed on the HCT/P 351 regulatory track. This is a costly and multiyear process involving application for approval of an IND culminating in a BLA or investigational device exemption. The IND is a process designed for pharmacological drug manufacturing that is not easily adaptable to autologous cell therapies. It remains a hurdle to the translation of stem cell therapies into the clinical setting. Recognizing these limitations, leaders at the FDA, citing the review by Toyserkani et al. [9], have outlined a pragmatic response to achieving a balance between patient safety and innovation regarding adipose-derived cells [10,11]. As presently structured, the risk tier approach suffers from the crucial flaw that it addresses only the HCT/P product and not the mode of delivery or the practitioner. It should be recognized that are actually three sources of risk that must be considered by patients undergoing cell therapy procedures. The first source of risk is the cell product itself. A recent review evaluated the international literature relating to ASC and SVF cell therapies [9]. From an initial database search for keywords ''ASC,'' ''SVF cells'' ''processed lipoaspirate,'' or ''adipose regenerative cells'' capturing $n = 1{,}132$ publications, a subset of $n = 70$ articles representing 1,400 patients met the additional inclusion criteria of performing human studies in any disease with either autologous or allogeneic adipose-derived cells up to December 31, 2016. It is noteworthy that only 10% of these studies were conducted in North America, whereas Europe (46%) and Asia (40%) accounted for the majority. Study designs were criticized for the lack of case-matched controls and lack of uniformity in the definition of adverse events. Only a handful of studies evaluated immunological responses to transplanted allogeneic ASC, such as the host production of antibodies directed against donor-specific antigens [9]. Indeed, in one such study, up to 19% of allogeneic ASC transplanted patients displayed antibodies [12], consistent with preclinical rodent studies demonstrating that allogeneic, but not syngeneic, ASC induced antibody production [13]. Although the evaluation of such immunological responses may indeed prove valuable, it is noteworthy that their clinical significance in this context is unknown, and that clinical trials that led to the FDA's clearance of an expanded access treatment program and Health Canada's Notice of Compliance with conditions (NOC/c) for the use of allogeneic transplant of the bone marrow MSC product ''Prochymal'' for the treatment of pediatric graft versus host disease did not mention any equivalent analysis of antibody formation [14,15].

The second source of risk is that the patient will not have a proper medical evaluation and that the practitioner performing any procedures has the appropriate technical skill and expertise. The ultimate example of this second risk is the aforementioned report of the three cases of blindness after SVF injection [3]. The injections were delivered in violation of commonly accepted American Board of Ophthalmology standards by an individual practicing without board certification in ophthalmology. Indeed, in this clinical scenario, even an FDA-approved product may have caused blindness. This is not a cellular product risk, but a practice of medicine risk.

The third source of risk is the facility in which the treatment is being carried out. Accreditation agencies such as American Association of Blood Banks (AABB) and Foundation for Accreditation of Cellular Therapy (FACT) are ideally suited to oversee ASC cell therapy facility operations as they presently do for other types of cell therapy facilities and blood banks. To use the ''wild west'' metaphor again, the FDA should not be the only sheriff on the job. If the root cause of the problem is medical treatments offered without regard to evidence and safety, a coordinated effort by multiple governmental and professional bodies is worthy of consideration. Although the FDA serves as the ''sheriff'' in situations involving evidence of therapeutic agent safety, state medical boards and specialty societies should step in to ''police'' rogue physicians/practitioners where questions relate to competence, scope of practice, and specialty accreditation.

Likewise, facility accreditation agencies such as FACT and AABB should step in in matters related to facility standard operating procedures and manufacturing practices.

Other concerned parties have taken alternative approaches to improve the balance between timely delivery of advanced therapies and patient safety. On the legislative front, the combined efforts of the Bipartisan Policy Committee (BPC) and the Regenerative Medicine Foundation (RMF) along with others led to the introduction of the new regenerative medicine advanced therapy (RMAT) pathway under the 21st Century Cures Act. The RMAT represents an expedited mechanism for review and potential approval of cell therapy products intended for serious or life-threatening conditions, and incorporates the consideration of preliminary and ''real-world'' clinical evidence toward addressing unmet medical needs.

The emphasis on preliminary clinical data addressing safety is particularly timely for two reasons. First it allows for the collection of data from legitimate investigators in the form of organized registries. More importantly, there are already federal funds allocated for the creation of such registries. The CW Bill Young Act has earmarked funds for the creation of an allogeneic stem cell registry, the Stem Cells Therapeutic Outcomes Database (SCTOD). This model has worked exceptionally well in the domain of bone marrow and related cell types, by helping to advance the practice of bone marrow transplantation and other cellular therapies in an ethical and scientifically valid way. The Center for International Blood and Marrow Transplant Research (CIBMTR) presently holds the contract to create and manage the SCTOD. The CIBMTR is currently in conjunction with the BPC and the RMF and other stakeholders, including International Federation of Adipose Therapy and Science (IFATS) and the American Society of Plastic Surgeons (ASPS), crafting the working details of implementing a national registry for regenerative therapies.

This coalition has had fruitful discussions with the FDA, in which the paramount role of the IND pathway was confirmed, but with modifications tailored to the emerging regenerative medicine landscape. This was reflected in a recent statement by then Commissioner Gottlieb in which the concept of ''group IND's'' was alluded to. This would allow groups of investigators who may not be of sufficient scale to conduct a full-fledged clinical trial to collect and pool data under a common IND (https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm629493.htm). This is a very welcome sign of flexibility from the FDA. The emerging strategy from the CIBMTR/BPC coalition is to target a few conditions for which regenerative therapies (including ASCs and SVF) have shown particular promise and incorporating them into an RMAT designation. A ''group IND'' will then be crafted under which several investigators may initiate studies, gather data, and incorporate it into a national registry for regenerative therapies.

These efforts address product safety, but the last unknowns in the emerging safety/innovation balancing act remain the practitioner and the clinic or facility setting. To paraphrase Dr. Marks (Director of CBER): How do we keep the scofflaws out? A reasonable answer is accreditation, a model that has worked well in the world of bone marrow and other cellular therapies. Both the AABB and FACT are well-established accreditation agencies that have published cellular standards that may be easily tailored to adipose-derived therapies (ASCs and SVF). In fact, IFATS is in the process of developing such facility accreditation standards for adipose-derived therapies with AABB. The accreditation process can directly address issues crucial to safety such as practitioner competence, scope of practice, and maintenance of adequate standard operating procedures. In this context, it is relevant to revisit the example of the three cases of blindness by SVF injection [3]. The safest way to deliver any specialized therapy, whether it is FDA approved or not, is by a physician who has received specialty training reasonably related to the disease being treated. In an accredited facility, a physician who was not board certified in ophthalmology or had hospital privileges to perform the procedure would have never been allowed to inject cell or other therapies into the globe of an eye. Furthermore, the incidents would have been audited by the accrediting agency, with repercussions to the facility well before their being discovered in the context of a lawsuit. Finally, adverse results would have been reported to a registry as required by other cellular therapy accreditations.

The authors fully endorse the FDA's goal of establishing safety and efficacy, as well as developing accelerated pathways for the development of regenerative therapies. As scientists, clinicians, and innovators, we are staunch advocates for the safe development of new regenerative therapies based upon solid evidence. We respectfully suggest a multipronged approach to both accelerating the development of new regenerative therapies and controlling the spread of unsubstantiated and unsafe therapies:

- Re-evaluate the regulatory and scientific rationale for the guidelines that categorize tissues as either structural or cellular under 21 CFR 1271. We recognize and approve of the need to evaluate carefully and methodically the safety and efficacy profile of SVF, but not at the expense of scientific fact and regulatory consistency. Autologous SVF therapy has a different risk and safety profile than that of cultured autologous or allogeneic cells.
- Support FDA attendance at scientific meetings to share information and promote dialogue with scientists and clinicians. Multiple national and international scientific/clinical societies routinely address the latest information relating to stem cell therapies; however, some societies such as IFATS have experienced challenges when inviting presentations by FDA representatives in recent years due to restrictions on federal personnel travel and related internal issues. Annual and consistent attendance by FDA staff, including leadership, at such regenerative medical meetings would facilitate dialogue and education in the clinical translational community.
- Work with accreditation agencies such as AABB and FACT to develop meaningful accreditation standards for facilities delivering adipose-derived therapies such as ASCs and SVF. Accreditation of facilities is the most effective way of ''keeping the rogue element out'' and ensuring that patients receive these advanced therapies in the safest environment, under a rigorous set of standard operating procedures that are independently reviewed periodically by the accreditation body. Accreditation agencies can also act as an enforcement agent. This lets the FDA focus on its primary role on determining drug and cell product safety rather than on rogue physician or clinic behavior.

- Work with professional societies and related organizations to develop a national registry for stem cell therapies. The BPC/RMF coalition to develop a national registry for stem cell therapies is well under way and is anticipated to garner access to federal funding. The FDA's input into desired datapoints for capture is invaluable as this captured data will dovetail with ''real-world data'' requirements set forth by the 21st Century Cures Act. The potential for FDA's participation in the development of a national registry for stem cell therapies is not without precedent as the FDA already participates with the AABB and FACT in the development of standards for accreditation of other cellular therapies.
- Accept the primary role of State Medical Societies and professional medical societies in regulating physician behavior. State medical boards have direct oversight of provider licensing and have disciplinary power. Moreover, they can set and enforce certification requirements for facilities. Often, stem cell clinics fall into a ''no man's land'' of oversight in which FDA oversight is either questioned or not yet enforced, and the state medical boards do not have reason to intervene. As originally suggested by Taylor-Weiner and Zivin [1], state medical boards play a critical role in monitoring and enforcing standards of medical practice. In Louisiana, the state medical board proactively convened a team of stem/stromal cell experts and clinicians to establish best practices regarding cell therapy. Their conclusions were publicized through the state medical board's website and highlighted the need to secure IRB approval and FDA clinical trial registration before initiating any stem cell therapies. It may prove advantageous to convene a meeting at the FDA with representatives from medical boards in all 50 states and U.S. territories to disseminate and exchange best practice information related to cellular therapy. Importantly, sharing information in such a form could lead state medical boards to standardize regulations regarding advertising and administering cell therapies. Specialty boards and societies are also committed to safe practice and hold the public trust. ABMS boards have rigorous certification processes and enforce standards through maintenance of certification requirements. Most professional specialty societies require board certification to maintain membership and also have a societal code of ethics. These bodies could work with a coalition of state medical boards and the FDA to set and enforce for diplomats and society members standards of practice that govern scope of practice and training requirements. Although ABMS boards and professional societies may not impact medical licensing directly, disciplinary action by such bodies may be reportable to state medical boards, and many hospitals require board certification to obtain active staff privileges.
- Link the posting of stem cell trials on clinicaltrials.gov to participation in a national registry for stem cell therapies and facility accreditation by AABB or FACT enrollment of any facility or practitioner into these entities ensures a seriousness of purpose with adherence to high standards of safety and accountability as a prerequisite to initiating care.

In summary, all major advancements in cell therapy have been accomplished with some practically unavoidable level of concurrent adverse events. The intent of such medical advancements has been to improve the greater good for patients and their families. To achieve this goal, the risk of therapy has always been thoroughly assessed, balanced, and applied in a manner commensurate with the severity of the underlying disease and its associated comorbidities. With this historical perspective, the authors of this commentary remain enthusiastic in their support of translational human studies advancing adipose-derived cell therapies in accordance with long-established requirements of ethical medical practice and regulation. With appropriate and coordinated federal, state, and private sector oversight, adipose-derived cell products will eventually be accepted nationwide as serving society's greater good.

Author Disclosure Statement

J.M.G. is the cofounder, co-owner, and chief scientific officer of LaCell LLC, a for-profit biotechnology company focusing on the clinical translation and research of stromal/stem cells; J.M.G. and T.F. are cofounders of Obatala Sciences, Inc., a for-profit ''fat on a chip'' company where T.F. serves as the president and CEO. C.A.M. is a former director of investigations for the Louisiana State Board of Medical Examiners; A.J.K., J.P.R., K.L.M., R.L., and J.M.G. are all board members of the International Federation for Adipose Therapeutics and Science (IFATS), a nonprofit scientific society. J.P.R. is a board member of the American Society of Plastic Surgeons, a nonprofit professional society, and an advisor and equity holder in RegnMed, which produces data systems for regenerative medicine therapies. A.J.K. is co-chair of the Regenerative Medicine Committee of the American Society of Plastic Surgeons, a nonprofit professional society; he is also a founder and board member of the GID Group, Inc., a for-profit biotech company focusing on the clinical translation of adipose-derived cells.

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