Evaluating the FDA regenerative medicine framework: opportunities for stakeholders

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Though stem cell products, gene therapies and other regenerative techniques have significant potential to 1-day treat traumatic injuries or serious disease, relatively few regenerative medicine products have been approved by the US FDA. However, this has not stopped hundreds of US businesses from selling unproven – and, in many cases, harmful – stem cell and regenerative interventions (SCRIs). Clinics around the world offer unproven SCRIs for a host of conditions to patients with few to no clinical options [1]. As of early 2017, there were estimates of 716 clinics offering SCRIs in the USA alone [2,3] – a number that has likely grown since then [4]. Using aggressive marketing primarily through patient testimonials and online information that is often exaggerated and incorrect, many clinics offer scientifically under- or untested interventions that have been shown to result in physical, emotional and financial harm [5–8]. Within the USA, there have been significant efforts made at the national, state and institutional level to regulate the market, educate physicians and inform patients. Most notable are the efforts made by the FDA in developing guidance to delineate more precisely which products would be required to go through the full drug development process, enforcing regulatory standards to curb the practices of riskier clinics and informing the scientific community and the public about responsible practices. Yet the smaller size of clinics, online nature of the marketing, limited resources of regulatory and oversight organizations and lack of overall coordination by multiple stakeholders has resulted in a patchwork of policy and regulatory efforts making it difficult for the FDA and other organizations to curtail the market [3,9,10].

It is for this reason that the Pew Charitable Trusts conducted an evaluation of the FDA’s framework and other policy approaches [10]. The goal of this project is to: understand how the framework was perceived among a select group of experts; describe any remaining areas of scientific or regulatory ambiguity that would need to be addressed; and identify next steps for FDA and other stakeholders to help ensure the safety and effectiveness of the regenerative therapies on the market. This evaluation included a formal legal analysis of the agency’s guidance documents and the relevant statutes, as well as a series of 11 interviews with expert stakeholders (including practicing physicians who perform clinical stem cell research, legal experts on the regulation of human cell and tissue products [HCT/PS]), a stem cell biologist and a bioethicist identified through purposive sampling. A full list of the interview subjects is available in the methodology section of the full report [10].

In this commentary, we will describe features of this market and highlight the findings to help inform scientists, manufacturers/sponsors and clinicians about the current regulatory space and enforcement climate. Because our analysis shows that FDA alone cannot fully protect the public from this rapidly growing market, we also describe

opportunities and next steps for other public health stakeholders with an interest in ensuring a market of safe and effective regenerative medicine products and service lines.

The current US regulatory & policy climate of regenerative medicine

The US market for unproven and unapproved SCRI has grown rapidly despite the fact that FDA has clear statutory authority to regulate human cells, tissues as well as therapeutic products derived from human cells and tissues (collectively referred to as HCT/Ps) [11]. The level of regulatory scrutiny applied to these interventions depends on the risks associated with a given product. For example, HCT/Ps that are removed and implanted into the same person during the same surgical procedure are not generally subject to FDA regulation, provided that the HCT/Ps are not manipulated in any way beyond cleaning, sizing or shaping. This is often referred to as the ‘same surgical procedure exemption,’ and it includes things like skin grafts or coronary artery bypass surgery.

Other HCT/Ps are exempted from premarket review, but are subject to regulations intended to prevent the spread of infectious disease – these products are often referred to as ‘Section 361 HCT/Ps,’ after the relevant section of the Public Health Services Act that outlines the rules that apply to them. These products must meet four key criteria:

- Be ‘minimally manipulated,’ a concept which the agency defines as processing that does not alter the ‘original relevant characteristics’ of cells and tissues and for which it applies different regulatory criteria depending on whether the tissue is structural or nonstructural.
- Be intended for ‘homologous use’ – that is, when an HCT/P performs the ‘same basic function’ in the recipient as in the donor.
- Not be combined with other substances, except in limited, specific circumstances.
- Not have a system wide effect or depend on the metabolic function of living donor cells in order to function as intended, unless the product is for a patient’s own use, is being donated to a first- or second-degree relative or is for reproductive use.

If an HCT/P does not meet the criteria for a section 361 product or the same surgical procedure exemption – for example, if it is adipose tissue that is extracted from a patient and processed into stromal vascular fraction before reimplantation – it must go through FDA premarket approval (Figure 1). Depending on whether the HCT/P meets certain statutory criteria, the developer may be eligible to receive expedited status through the Regenerative Medicine Advanced Therapy designation, which is a regulatory pathway that is intended to facilitate the development and review process.

In November 2017, the agency released four new guidance documents that together make up its current regulatory framework for regenerative medicine [12–15]. At the time of publication, the agency also announced a 3-year period of enforcement discretion for manufacturers of certain HCT/Ps that were already on the market, which is due to end in November 2020. This move was intended to give these companies time to consult with the FDA about their products and, if necessary, to begin moving them through the formal development and approval process.

At the same time, the agency noted that it would continue to pursue legal and regulatory actions against businesses marketing illegal products that threatened public health. The agency has since sought formal injunctions against two companies – one of which was granted; the other is still pending trial – and sent warning, untitled and other letters of correspondence to dozens more [16]. It has also taken a number of steps designed to facilitate the drug development process, including establishing a temporary program that allows manufacturers to obtain an informal, nonbinding assessment of whether their products will be required to file Biologics Licensing Application [17].

Despite these efforts, hundreds of clinics continue to market unproven and unapproved stem cell products directly to patients. These providers often claim that their products treat countless medical problems from arthritis to autism and multiple sclerosis. While there is little to no sound evidence that these products help patients, there are many examples where patients were harmed [18].

Opportunities to clarify FDA oversight

Pew’s evaluation found that FDA’s framework was generally perceived to be an efficient, risk-based approach to regulating the industry and was appropriately rigorous. Most interviewees agreed that it provided important clarity on how the agency would regulate HCT/Ps, but noted some remaining ambiguity regarding HCT/Ps that are

Figure 1. The level of FDA review applied to human cell and tissue products depends on several key parameters: whether the product meets the formal regulatory definition of an HCT/P; whether it meets the requirements for the same surgical procedure exemption, and if not; whether it meets the four criteria that allow it to be regulated solely under Section 361 of the Public Health Services Act and Part 1271 regulations, which are aimed at preventing disease transmission. If the product does not meet these qualifications, then the FDA will regulate it as a biological product and require the developer to submit a biologics licensing application.

HCT/P: Human cell and tissue product; PHS: Public Health Service.

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transplanted within the same surgical procedure. Under that guidance, it remains unclear how the agency will approach products that remain in their original form but are used in a surgical procedure in ways that may deviate from their original function; for example, if a patient's own bone marrow stem cells are isolated and then used to treat, say, a neurological condition. Moving forward, the agency may want to provide additional examples – possibly in updated guidance documents – of how such products will be classified and regulated under the framework and update existing regulations as more products come through the development pipeline.

Longer-term challenges for regulators

There are more than 1000 regenerative medicine products in clinical trials worldwide, most of which are now in Phase II development [19]. The agency will need additional resources as well as adequately trained staff to handle the growing number of applications it will need to review [20]. In 2018, then Commissioner Gottlieb called for 50 additional reviewers for the Center for Biologics Evaluation and Research to help address the workload. But it will likely be challenging to attract and retain staff with the requisite level of expertise given the competing private-sector demand. And though the 21st Century Cures Act gave the FDA new hiring authorities designed to attract experienced professionals, there are still hundreds of vacancies across the agency [21].

The larger challenge, however, relates to the agency's efforts to enforce its regulations against businesses offering unapproved and potentially dangerous SCRI to patients. While the 3-year period of enforcement discretion was intended to give legitimate businesses time to come into compliance with regulations, it also allowed the number of noncompliant actors to continue operating and potentially expand. It will be impossible for the agency to inspect them all, let alone bring legal cases against these providers. And it remains unclear how successful the agency will be in stemming their spread. The two stem cell firms that received legal injunctions in 2018, for example, continue to operate despite the agency's court victory last year. Others may simply move their operations outside of the

USA [22]. But even though the agency cannot target all businesses that are violating the law, it can do more to target those engaged in particularly high-risk practices. The FDA can also seek out ways to support the efforts of other regulators and public health stakeholders who have a role to play in ensuring patient safety and protecting the legitimacy of the field more broadly.

A potential role for other stakeholders

There are opportunities for other regulators at the federal and state level to play a substantial role in halting and eventually reversing the spread of dangerous stem cell clinics. Both the Federal Trade Commission and state attorneys general can explore and pursue charges against clinics that engage in false and misleading advertising, as they have done in recent cases in California, Iowa, Nebraska, New York and North Dakota [23–25].

State governments can also help to protect patients by legislating in favor of stricter oversight. At least nine states have already introduced or passed legislation related to stem cell clinics, though it is unclear if any best practices have emerged, and not all state actions have been geared toward stronger patient protections [26–29].

State medical boards, which govern medical practice and can take disciplinary action against providers, could conduct proactive investigations of the clinics in their jurisdiction that offer risky regenerative and stem cell therapy treatments to patients and regularly monitor databases such as the National Practitioner Data Bank and the Physician Data Center, which harbor information on providers who have been the target of previous malpractice suits or disciplinary action [30,31]. The FDA can also assist in this effort, either by submitting warning letters to these databases or directly sending them to the relevant medical boards to inform them when the agency has raised concerns about a provider's practices.

Individual or class action lawsuits have also been undertaken by patients who have suffered damages, with claims including physical suffering, emotional distress, false advertising, misrepresentation and a lack of informed consent, among others [7]. This kind of civil litigation can help plaintiffs seek restorative justice and compensation for injuries and may also help to drive broader change in the industry by uncovering harmful business practices, raising public awareness about unapproved SCRI through the media and pushing more businesses to comply with FDA regulation and other applicable laws. Civil litigation can also help facilitate FDA investigation if the discovery process in patient lawsuits is tried and reveals undisclosed violations of the law.

However, stem cell clinics have also used the threat of legal action, often to push back against criticism. In 2011, for example, the International Society for Stem Cell Research (ISSCR) launched a 'Submit a Clinic' website in an effort to better inform patients considering an SCRI. Patients were invited to submit advertisements by specific clinics or providers, which ISSCR proposed to examine more closely to help ensure there was appropriate oversight of the clinic. This information would then be posted to the ISSCR website [32]. Clinics quickly challenged the authority of the society to conduct such investigations, resulting in ISSCR abandoning the project to avoid possible legal action [32,33].

Improving education & limiting the spread of misinformation

There are also a range of cross-cutting interventions that could help to reduce the spread of misinformation surrounding the regenerative medicine field and improve informed consent practices for patients seeking such therapies. While many scientific organizations have played a significant role in attempting to improve information for patients and the general public, overall these efforts have been sparse. Most patient education has been in the form of online information on websites and patient handbooks and videos [34–41]. One recent study has shown that online resources may influence one's intention to consider a riskier unproven SCRI, albeit for a short time after reading the resource [42]. Considering the market is driven by misinformation and patients are avid information seekers [43–48], there is a need for more accurate patient education as well as interventions designed to elicit health behavior change [49].

More recently, two studies have examined the nature of expert consultations to inform patients about SCRI. Both Stem Cells Australia, a stem cell science initiative established by the Australian government and EuroStemCell, a reliable source of information on SCRI, offer online and caller platforms to address patient queries about SCRI related to their conditions [48]. In 2011, Mayo Clinic established the Regenerative Medicine Consult Service that provides information and navigates patients to evidence-based SCRI [45,47]. Strategies of patient counseling are likely to be tremendously helpful to address patient questions and concerns about SCRI and patient booklets and online information can complement such efforts to help correct misinformation.

In addition to patient education, efforts should also be made to better inform physicians about the science behind these interventions, including their risks [50,51]. About half the physicians providing unproven SCRI are unqualified [9,52] but continue to offer them to patients regardless. Several organizations have entered the business of teaching physicians how to apply stem cell interventions to patients. It is not always clear whether such training is intended to prepare physicians for entering research or practice, but some advertisements do discuss the prospects of profit and patient demand over SCRI [53]. While there have been legitimate efforts to educate medical and science students about stem cell and regenerative medicine, [54–56], aside from one report by the International Society for Stem Cell Research [57], there has been no continuing medical education or other training developed to educate practicing physicians considering getting into the stem cell business.

Online and other forms of education and counseling can further complement regulatory and policy efforts to ensure regulatory compliance in business practices and provide information and correct misinformation for patients, physicians and the public. Online advertising platforms can also take steps to reduce the spread of misinformation related to SCRI. Google, for example, recently banned advertisements marketing unapproved medical therapies, including SCRI [58]. Other companies that serve as advertising platforms should consider following their lead.

Conclusion

While progress has been made by the FDA on implementing the various components of the new regulatory framework, its impact on the regenerative medicine industry – and on the successful development of safe, effective and innovative new therapies – remains to be seen. For FDA to succeed in its efforts in bringing the industry into compliance, it will be important for the agency to continue prioritizing oversight and enforcement. However, given the size of the current market for these products, addressing the problem will require a combination of different interventions targeting a range of audiences and stakeholders in the federal, state and private sectors.

Summary points

- Human cells, tissues and cell- and tissue-based products (HCT/Ps) – which play a key role in the field of regenerative medicine – may have the potential to treat a range of medical illnesses and conditions, but relatively few have been approved by the US FDA.
- However, the market for unproven and unapproved stem cell and regenerative interventions (SCRI) is large and growing, posing a risk to public health and potentially undermining public confidence in the regenerative medicine field.
- In 2017, the FDA released an updated regulatory framework that aimed to clarify its policies regarding the regulation of HCT/Ps and in particular, how it would determine which products would be subject to full premarket review.
- In order to give manufacturers time to come into compliance with this framework, the agency also announced a 3-year enforcement discretion period, which will end in November 2020. During this time, the FDA is enforcing its regulations only against those products that pose a significant safety concern.
- Interviews with a range of experts revealed that FDA's framework is science-based and provides helpful clarity for the field, but that additional clarity is needed with regard to how the agency will regulate certain interventions. Interviewees also raised concerns about FDA's ability to adequately enforce its framework given the number of businesses currently offering unapproved and risky SCRI.
- There is substantial opportunity for other public health stakeholders to play a role in protecting patients from harmful products. This includes legal action by federal and state agencies like the Federal Trade Commission and state attorneys general offices; state legislation to tighten regulation of clinics; better oversight by state medical boards; and individual private action against clinics.
- Scientific and professional organizations can also take steps to improve both patient and provider education about unapproved SCRI and increase awareness about their risks. Companies that manage online platforms can support these efforts by doing more to limit the spread of misinformation and prevent clinics from advertising their products on their platform.

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