Direct-to-consumer (DTC) advertising of suspect goods and services has burgeoned because of the Internet. Despite very limited approval for use, DTC stem cell–marketed "treatments" have emerged for an array of conditions, creating global public health and safety risks. However, it remains unclear whether such use of stem cells is subject to drugs or biologics regulations. To address this gap, regulatory agencies should be given clear authority, and the international community should create a framework for appropriate stem cell use. In addition, consumer protection laws should be used to scrutinize providers.

THE DTC DEBATE

Stem cell therapies are being advertised DTC—for everything from breast augmentation to genetic diseases to spinal cord injury—by providers in developed countries (such as the United States, United Kingdom, Japan, and Germany) and in emerging markets (such as Mexico, China, and Russia). DTC marketing for stem cell therapy is highly troubling, given the documented patient safety risks arising from suspect claims, unknown treatment protocols, limited follow-up, and potential for serious adverse medical events. Medical risks include the possible transmission of infectious and genetic diseases, uncontrolled cell or tumor growth, and immunogenicity, any of which can result in death. Questions regarding the consistency and quality of stem cell therapies, including concerns of whether therapy contains actual stem cell products or is otherwise substandard, as well as questionable sourcing of biological material used in treatment, have cast doubts on this burgeoning industry.

If used in an ethical manner, DTC promotion has the potential to provide benefits to patients by promoting patient participation in clinical decision-making, informing patients about existing treatment options, and improving patient adherence to therapy. But inflated DTC stem cell marketing uses suspect patient testimonials and claims mostly unsupported by the medical literature in order to promote "innovative" therapies without adequately providing balanced risk versus benefit information. The risks associated with unapproved treatments are exacerbated by Internet-based forms of DTC marketing—Web sites, social media tools, YouTube, blogs—that enable providers to market to and recruit thousands of patients globally at little cost.

In addition to health risks, DTC stem cell therapy can be extremely costly, with reported estimates averaging $47,000 per treatment. Vulnerable patient populations—including use in minors—have fueled the growing phenomenon of "stem cell tourism," in which prospective patients travel to countries that offer therapies not approved in their home jurisdiction. Indeed, three individuals were prosecuted recently for illegally manufacturing, selling, and performing stem cell treatments from which they netted more than $1.5 million from patients seeking treatment for incurable diseases. Although there has been closure of clinics engaged in potentially illegal activities, enforcement efforts have been mostly ineffective owing to regulatory ambi-

REGULATORY SCIENCE

Stem Cells, Dot-Com

Bryan A. Liang†,‡,§ and Tim K. Mackey†,¶

Direct-to-consumer (DTC) drug advertising has been shown to adversely affect patient safety and public health and, via Internet technology, has gone global. Digital DTC advertising now crosses borders, potentially inducing unnecessary demand for medical treatments, increasing national health care expenditures, and promoting therapies with questionable safety and risk profiles.

Yet, global DTC is expanding and now promotes experimental stem cell therapies offered by several global purveyors, including RegeneCell (Mexico and India; www.regene-cell.com), ASCI Regenerative Stem Cell Therapies (www.stem-cell-center.com), Stem Cell Institute (Panama; www.cellmedicine.com), Beike Biotechnology (China; http://stemcelltreatmentnow.com), and International Stemcell Services Ltd. (India; www.internationalstemcellservices.com).

These largely unregulated actors often promise prospective patients clinical miracles and beneficial treatment outcomes for various organ systems and diseases—anywhere from autoimmune to cardiovascular to neurodegenerative—despite the fact that the vast majority of these therapies are experimental and not approved by drug regulatory agencies (DRAs). Stem cell therapy is only clinically accepted for a handful of disease states—for example, bone marrow transplants after chemotherapy—and the U.S. Food and Drug Administration (FDA) has not approved any stem cell–based products for use other than cord blood–derived products for specific indications.

Fraudulent and misleading online DTC marketing of stem cell therapies now entices patients worldwide to try experimental treatments with poorly defined reagents. Here, we assess the digital DTC stem cell therapy landscape and limitations of the current regulatory environment and then propose strategies to rectify this complex situation.

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guity and operations located overseas, with some clinics closing as a result of bad press, not direct regulatory action (6, 9).

**REGULATORY LIMITATIONS**

Currently, there is regulatory conflict in stem cell marketing, processing, and use. In the United States, District courts in Washington, DC, have recently ruled that the FDA now has the statutory authority to regulate certain stem cell–based products and treatments. However, this controversy persists in other countries—and indeed, still in the United States because the recent court decision can be challenged. Specifically, ambiguity regarding the role of stem cell DRA regulation as a drug, biologic, device, or human cells, tissues, and cellular and tissue-based products (HCT/Ps) (depending on the specific stem cell–based product or therapy) continues to conflict with interpretations that such use falls under regulation as the practice of medicine (defined generally by state medical boards as the diagnosis, cure, prescribing, or advising for any human disease, injury, deformity, pain, alment, or other condition physical or mental).

In attempting to exercise the apparent authority of DRAs over stem cell therapy, the FDA sought termination of DTC advertising of stem cells by a domestic provider. This includes the recent court ruling in FDAs favor for summary judgment and a permanent injunction against a stem cell clinic in the U.S. federal case *United States v: Regenerative Sciences*, on grounds that the provider’s stem cell treatments (Regenexx Procedure, www.regenexx.com) constitute the manufacturing of a drug/biologic product. These enforcement efforts are based on DRA arguments that forms of stem cell–based products and therapy—including clinical harvesting, cell culture expansion, and reinfusion into patients—are subject to existing FDA drug regulation. Under this interpretation, such stem cell use must generally gain FDA approval to ensure safety and effectiveness for intended use before they can be marketed. In addition, stem cell–based products containing cells or tissue that are either highly processed, used outside of their normal function, combined with nontissue components, or used for metabolic purposes require submission of an investigational new drug (IND) application and are regulated as biologic products subject to current good manufacturing practices (cGMPs) (11). Hence, DTC stem cell marketing and therapy, which may promote unapproved or unregistered therapies and products, can be deemed misbranded and adulterated because they fail to meet these DRA requirements.

However, further confusing the scope of regulatory authority, different product categories for HCT/Ps exist under current FDA regulations. Specifically, DTC stem cell providers may claim that their products fit the definition of “minimally manipulated” (processing that does not alter the relevant biological characteristics of cells or tissues) and are homologous [used to perform the same basic function (or functions) in the stem cell therapy recipient and donor]; these products may not be subject to FDA approval (14). Attempting to take advantage of this narrow definition, companies such as Regenerative Sciences (www.centenoschultz.com, Colorado, United States) have argued that their stem cell procedures, including Regenexx, are autologous uses of HCT/Ps and fall under the practice of medicine (12). Although the recent District court decision has reestablished FDA authority over this procedure, news reports (15) reveal that the medical director plans to continue to make available other stem cell procedures not subject to the injunction and make Regenexx available outside of the United States. Yet, there are only very limited circumstances that may allow physicians to administer stem cell–based products that are manipulated, including compassionate-use cases, off-label prescribing of FDA-approved stem cell products, and same-surgical procedures (14).

Most countries in the world (such as the United States, India, Canada, Ireland, and Australia) also use independent national or state entities—such as Medical Councils made up of medical leaders, practitioners, academics, and public health and ministry of health officials—charged with regulating the quality of medical practitioners, their education, accreditation, and services separately from DRA oversight of drug and biologic safety (11, 12). Because a majority of jurisdictions have this structure, it is likely that those that fail to specifically regulate stem cell therapy will face similar legal arguments when attempting to regulate inappropriate marketing and stem cell use that is not reviewed and approved by DRAs.

Further exacerbating this regulatory conflict is questionable self-regulation by certain members of the stem cell industry in the absence of proactive DRA oversight. This includes the International Cellular Medicine Society (ICMS), which offers accreditation of stem cell providers and clinics (8, 11). However, its physician-member application does not appear to require credential verification, and its clinic membership does not require Institutional Review Board (IRB) approval because the ICMS sells its own IRB services. This presents many conflicts of interest and can potentially mislead patients regarding the authenticity and safety of DTC-offered stem cell treatments.

**REGULATORY REFORM**

Given the regulatory and safety challenges and the urgent need to protect patients, steps to curb misleading and fraudulent DTC advertising and unregulated use of stem cell therapy should take priority in enforcement efforts.

**Clarifying DRA regulatory authority.** Recognizing the potential conflict in regulation of stem cells as drugs or biologics versus the practice of medicine, DRAs must be explicitly empowered to independently define what constitutes the appropriate criteria of “minimally manipulated” and nonhomologous use of stem cell products when such authority is not sufficiently clear. Legislation and guidance could provide DRAs with presumptive authority to inspect stem cell provider facilities in order to determine whether stem cell products are more than minimally manipulated and are hence subject to premarket approval and cGMP and Good Tissue Practice requirements consistent with the recent court ruling against Regenerative Sciences. This should include strict identification of what stem cell uses fall outside these requirements—such as skin engravings and autologous stem cell transplants—and require DRA approval before use that does not fall under prescribed safe harbors. Legitimate stem cell–related research and use by academic medical centers that have undergone appropriate clinical trial registration and site inspection should be differentiated from illicit providers and given access to potential safe harbors to avoid unduly limiting innovation.

Indeed, some countries have taken proactive measures to specifically regulate stem cell therapy, including the United Kingdom in 2007 [Human Tissue (Quality and Safety for Human Application) Regulations] and Australia in 2011 (Therapeutic Goods Administration Regulatory Framework for Biologics). For example, Australia’s Regulatory Framework on Biologicals specifies that human stem cells are biological products and must be regulated according to...
risk and the extent to which they are manipulated (16). Ministry of Health officials in China recently called for a ban on clinical use of unapproved stem cell therapies in an attempt to better regulate domestic growth of this industry, although these efforts largely appear to be unsuccessful (17).

Further clarification and policy-making would proactively subject stem cell therapy providers to DRA authority and establish that the practice of medicine does not preempt DRA regulatory oversight. Successful regulatory approaches by DRAs can be shared to promote harmonization and discourage risky stem cell medical tourism.

DTC marketing regulation and disclosures. Given that DTC marketing is only allowed in a few countries and is a driving source for consumer demand, the curbing of exploitative marketing must be more vigorously enforced. Comprehensive DTC marketing regulation should include two components: (i) mandating robust public disclosure of stem cell therapy information, and (ii) active enforcement and prohibition against forms of false and misleading marketing claims.

As a standard, disclosures should include information proving that stem cell therapy providers adhere to applicable clinical trial registration requirements, IRB approval, patient-informed consent, pre- and post-trial follow-up, adverse event reporting, testing stem cell purity and potency, and screening and tracking of stem cell products (11). Stem cell providers would disclose clinical trial registration information (when required), DRA approval of stem cell products/therapies (if applicable), and provide evidence-based risk-versus-benefit information. All of this information should be available online to prospective patients as well as the public.

DRAs should also use existing legal powers to stop illegitimate online claims by stem cell marketers, including indictments against them for false and misleading statements and claimed treatment benefits. As an example, the FDA has the authority to review prescription drug advertising and promotional labeling to ensure that it is not false or misleading. The FDA also engages in review of all forms of DTC marketing through its Office of Prescription Drug Promotion. Given the specific risks posed by stem cell DTC advertising, the FDA could issue guidance requiring explicit presubmission of any form of stem cell DTC content prior to use for FDA review subject to harsh penalties for noncompliance, to ensure it does not involve unapproved products or indications. For violating Web sites, the FDA could issue warning letters outlining that stem cell therapies have not been evaluated by the FDA, may be associated with serious safety concerns, and that providers are in violation of federal laws regarding unproven claims as have been publicly issued for other unapproved drugs and devices. Healthcare professionals and patients should also be empowered to report suspected providers. The FDA could also invoke its powers to bring ex parte hearings (abbreviated hearings with only one side present) for temporary restraining orders (TROs) against Web sites potentially violating the Federal Food, Drug, and Cosmetic Act (4, 18). Under a TRO, patient protections against suspect sites may be put into place until full hearings can occur.

General consumer protection laws in individual countries that protect against deceptive and misleading advertising should also be leveraged against DTC stem cell marketing. In the United States, the Federal Trade Commission (FTC) and individual states can bring enforcement against claims made in product advertising by seeking injunctions, cease and desist orders, enforcement of civil and criminal penalties, and requiring issuance of refunds (19, 20). In fact, the FTC and FDA have acted against Web sites offering fake treatment and prevention products for severe acute respiratory syndrome (21). Indeed, the FTC, under Sections 5 and 12 of the FTC Act, has the authority and is actively involved in combating various forms of Internet health fraud, in partnership with the FDA (22). Similarly empowering national laws include the Australian Competition and Consumer Act (23) and the UK Consumer Protection from Unfair Trading Regulations (24). These laws should be used to reduce the number of questionable DTC stem cell providers and reinforce global proscriptions that prohibit DTC marketing. Importantly, exemptions should be put into place for legitimate use of DTC marketing by accredited research centers that will use advertising for patient recruitment and public education, provided such research is in compliance with applicable laws and regulations.

Regulators and enforcement agencies should work with international partners to shut down Web sites that use DTC advertising outside of FDA/FTC or other DRA jurisdiction. In the process, these agencies should also provide consumer education and work with Internet service providers and law enforcement to proactively shut down illegal providers, as they have in the past for illicit online pharmacies that sell counterfeit medicines (4, 25, 26).

Medical licensure oversight. Errant practitioners who engage in unsupported, unauthorized experimental stem cell use should be targeted through existing national or state medical licensure boards. Medical practice regulators and societies should act with dispatch against these health care providers and immediately suspend and move against their licenses. In the United States, state authorities have this power (5, 27), as do most countries in Europe (28). As an example, the Thai Medical Council recently drafted specific recommendations for stricter oversight of stem cell treatments by physicians (6, 7). The British General Medical Council also took action against a physician for administering inappropriate human adult stem cell treatments in 2010 (29).

Global governance. The global community of researchers, policy-makers, DRAs, public health agencies, patient-safety advocates, and other civil groups should create a framework for preventing unauthorized stem cell experimentation and marketing, similar to the International Society for Stem Cell Research (ISSCR) efforts to establish responsible, ethical guidelines in stem cell research (7, 30, 31). These efforts should include standardizing stem cell clinic operations and developing substantive and independent accreditation that includes human research protections. The ISSCR as an international society has worked to develop rigorous guidelines for evaluation and oversight, informed consent, and increased transparency for stem cell therapy. This represents a crucial first step in addressing the need for appropriate global oversight of unproven stem cell therapies and DTC stem cell claims. Without proper global regulation, harmonization, and enforcement, those who seek to exploit the most vulnerable and desperate patients will undermine legitimate research and scientific progress in stem cell–based therapy.

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