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Oversight for Clinical Uses of Autologous Adult Stem Cells:

Lessons from International Regulations

Dr. Tamra Lysaght
Senior Research Fellow, Asia Research Institute
National University of Singapore, Singapore 259770

A/Professor Ian Kerridge
Director of the Centre for Values, Ethics and the Law in Medicine
University of Sydney, Sydney NSW 2050
Bone Marrow Transplant Physician, Haematology Department
Royal North Shore Hospital, Sydney NSW 2065

Douglas Sipp
Unit Leader, Science Policy and Ethics Studies Unit
RIKEN Centre for Developmental Biology, Kobe 650-0057

Gerard Porter
Lecturer in Medical Law and Ethics, School of Law,
University of Edinburgh, Edinburgh EH8 9YL

Dr. Benjamin Capps
Assistant Professor, Centre for Biomedical Ethics
National University of Singapore, Singapore 117597

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Abstract

Autologous adult stem cells (ASCs) are being administered by physicians for indications that have not been demonstrated as safe and effective in formal clinical trials. Examination of regulatory frameworks across five countries suggests that balancing the demands of research with clinical freedom has created structural weaknesses that are being exploited.

Introduction

Although well-supported clinical applications of stem cells remain relatively few in number (Daley, 2012), the use of ASCs in advance of evidence from clinical trials has become increasingly prevalent (Bianco, 2013). Once mostly limited to countries lacking the regulatory infrastructure needed to monitor and control the claims made by healthcare professionals and institutions operating within their borders (Kiatpongsan and Sipp, 2008), these practices have also emerged in places such as the United States, Australia and Japan (Lysaght et al., 2014). The global proliferation of these practices raises serious concerns about the exploitation of vulnerable patient populations, the regulation of novel cell-based therapeutics, and the governance of medical professionals.

However, these practices appear less prevalent in some countries with similar standards in healthcare, scientific investment and economic structure to the US, Australia and Japan – Singapore and the United Kingdom are examples. This disparity suggests that there may be differences in the regulatory systems that oversee clinical uses of autologous ASCs in these countries that may be encouraging or discouraging their use outside the context of clinical

trials. To investigate this possibility, we compared the regulatory regimes of the United States, Japan, Australia, Singapore, and the United Kingdom (as a Member State of the European Union), with the aim of identifying similarities and differences in how autologous ASCs are regulated and governed within clinical contexts. We found that while there are many technical differences in language and implementation, broad similarities in the general regulatory approach suggest that there is no one explanation as to why these practices are more prevalent in some countries with apparently well-developed regulatory frameworks.

Regulation of Stem Cells in Research

All five countries examined have generally supportive environments for basic scientific research using stem cells, with some differences for lines derived from human embryos (Ishii et al., 2013). More importantly, they have all adopted risk-based approaches that regulate the use of stem cells in *clinical research* as either biological drug products or as medical procedures. In all of these countries, cell and tissue-based products (CTPs) that are regulated as drugs and/or biologics fall within the jurisdiction of a centralized government agency that controls the marketing of drugs, medical devices and biologics within each jurisdiction (listed in Table 1 along with relevant laws and regulations reviewed in this analysis). Such products are controlled through mandated premarket testing for safety and efficacy in specified indications, which typically involves a sponsor obtaining an Investigational New Drug (IND) designation and conducting a series of registered multiphase

(I–III) clinical trials. Subsequent market authorisation may include additional requirements for post-market surveillance.

Yet, these requirements only apply to products that are assessed as having higher than minimal risks, the definition of which varies across jurisdictions. Each country has exemptions that exclude from regulation autologous cells that have not been manipulated extensively or combined with other articles, are intended for homologous use in functionally compatible tissues, and/or are harvested and transplanted as part of the same surgical procedure. For example, haematopoietic stem cell transplants using autologous grafts for the reconstitution of bone marrow function are not regulated as biological drugs in any of these jurisdictions. Details about the level of manipulation and intended use of the cells vary across jurisdictions, and the definitions used to describe these processes are often ambiguous or undefined, but there is a general consensus that such products do not pose serious safety problems and are thus subject to relatively limited regulatory oversight. However, what constitutes 'homologous use' is not clearly defined in any of the regulations (listed in Table 1) and examples of processes that constitute 'non-substantial' or 'minimal' manipulation, where stated, are not exhaustive and differ from country to country. Variations may therefore arise in which cells are classified as 'minimal risk' and which are categorized as requiring greater regulation in different countries.

Even for highly manipulated products that are regulated as drugs, clinical trial sponsors and registered practitioners may apply to special programs that speed the approvals process or provide patients in exceptional circumstances with access to medicinal products that lack

the evidence necessary for market licensing. These programs differ in name and some of the conditions vary across jurisdictions. For example, so-called "compassionate use" or "special access" provisions, such as the *Expanded Access Program* in the US provide patients with access to experimental agents that are subject of an active IND, and personal importation policies such as the *Named Patients Access* program in Japan allow, in exceptional cases, importation for individual use of drugs that have been approved in another country. In contrast, no such restrictions apply for the *Special Access Scheme* in Australia, or the *Specials Scheme* and *Hospital Exemption Scheme* in the UK. Singapore does not have a formal access program but, as indicated below, registered practitioners operating in licensed hospitals may, at least in theory, offer unlicensed drugs to patients under their care.

Regulation of Stem Cells in Clinical Practice

The use of CTPs that are excluded from regulation as drugs (e.g. minimally manipulated autologous cells intended for homologous use), along with registered products that that are prescribed 'off-license' or 'off-label', are regulated as medical practice, rather than as medicinal products. In all five countries, the practice of medicine is not overseen by a central regulatory agency, but is regulated separately under complex frameworks of medical licensing boards, health departments and ministries, professional accreditation bodies, third party payers, and negligence laws (Taylor, 2010). Thus, while the laws around advertising medicines vary in each jurisdiction, practitioners may lawfully prescribe CTPs for indications that have not received pre-market approval within the discretion of their professional

judgment. Where an intervention falls outside the accepted standard of care, practitioners generally need adequate justification and may require special permission from an institutions' clinical practice or governance board. If the intervention is prescribed as part of a research protocol, then they may also need approval from an institutional review board (IRB). However, no permission or oversight is required from the authorities that regulate the marketing of medicinal products in any of these jurisdictions.

In addition, four of the five countries have laws that explicitly allow the manufacture of CTPs under the supervision of registered practitioners. In compliance with Article 3(7) of the Advanced Therapy Medicinal Products Directive (2001/83/EC) of the EU, the UK excludes from regulation any CTP that is "prepared on a non-routine basis" for use in a hospital under "the exclusive responsibility of a medical practitioner […] for an individual patient". This 'hospital use exemption' applies to other EU Member States, but has been implemented differently according to local interpretations of key terms, such as 'non-routine', leading to the exemption being applied more liberally in some countries (Mahalatchimy et al., 2012). The European Commission is thus currently considering the scope and application of the directive following public consultation in December 2012 (see web resources).

The UK has also enabled the *Specials Scheme* under the *Medicines Act* (1968) and the *Human Medicines Regulations* (2012), which provides exceptions for medicinal products, including CTPs, that are manufactured under the supervision of a registered medical practitioner, or by external vendors under a 'specials' license that is obtained from the Medicines and Healthcare Products Regulatory Agency. Singapore has similar exemptions in

the *Medicines Act* (1975, revised 1985) for the preparation of medicinal products by or under the supervision of registered practitioners operating within hospitals licensed under the *Private Hospitals and Medical Clinics Act* (1980, revised 1999). In Australia, autologous cells that are manufactured and administered by a registered medical practitioner (or under their supervision) for a patient under their care are excluded from regulation under the *Therapeutic Goods Act* (1989) in the *Therapeutic Goods (Excluded Goods) Order No. 1 of 2011*.

In Japan, drugs that are administered within the scope of a 'physician's discretion' in medical practice falls under the *Medical Practitioners Law (1948)* and are not regulated by the Pharmaceuticals and Medical Device Agency. Practitioners using autologous ASCs need to observe the *Practice Notice: Conducting Regenerative and Cellular Medicine Using Autologous Cells and Tissue at Medical Institutions (2010)*, but this only requires approval from an internal review board. A new law is currently being proposed that will clarify the extent of freedom licensed physicians have to prescribe unlicensed CTPs within their 'physicians discretion'. If enacted, medical institutions that offer these products will be required to register with the Ministry of Health, Labour and Welfare. However, following a risk-based approach, the law will only require full ministerial approval for pluripotent stem cells while IRB approval will suffice for somatic stem cell-based products.

In these contexts, the manufacture of CTPs must generally comply with current Good Manufacturing Practices (or Good Tissue Practice if not classified as drugs), but their use is otherwise regulated as clinical practice, not research. The exception is the US, where the

manufacturing of biological drugs is controlled solely by the Food and Drug Administration (FDA), which has no such exemptions for medical practitioners to make and supply their own drugs. However, the FDA's jurisdiction only applies to products, or ingredients that make up those products, that are shipped across state borders; the question of whether this authority extends to products made with ingredients sourced and delivered entirely within state borders, but which compete with products sold in other states, remains unresolved (Koustas and Fleder, 2011). Regulation of these products presumably falls under the jurisdiction of the medical boards and health departments in each American state.

Structural Weaknesses and the Challenge for Regulators

Despite the many technical differences in implementation and nomenclature, the general approach in all five countries is to provide a clear evidence-based pathway for CTPs that are regulated as medicinal drugs while allowing patients to access low-risk interventions with autologous ASCs under the supervision of their physician. This approach is designed to provide protections for research subjects while maintaining clinical autonomy for medical professionals and their patients. To support these goals, all five jurisdictions have implemented risk-based approaches to the regulation of CTPs, giving regulators a degree of flexibility in determining the level of oversight and standards of evidence that should apply before these products are introduced onto the market. However, as their use in clinical practice is largely unregulated, the approach also creates structural weaknesses that may be exploited by unscrupulous operators.

A key challenge that regulators face in addressing these weaknesses is ensuring that patients have the freedom to access novel interventions, while accommodating the inherent uncertainties of clinical research. Where uncertainty is a key characteristic of science – and regulations, ethical guidelines and governance processes can be designed to minimize harms that may arise from it – regulating clinical decisions in the face of such uncertainty is often more difficult. Across all five jurisdictions, regulators and policymakers are generally reluctant to interfere in decisions that many would argue should remain within the doctor-patient relationship. Yet, while historically this has been politically and culturally acceptable, few would agree that physicians should be permitted *carte blanche* authority in their practice of medicine, unchecked by accountability to their patients or the social systems that ultimately provide their healthcare. Balancing professional and patient autonomy with the need to provide therapies that are evidence-based, yield a meaningful benefit and are affordable to the community may, therefore, create a potentially intractable problem for regulators and policy-makers.

Regulators do have power to control unethical and illicit clinical practices, however, and a number of mechanisms may be employed to control the use of autologous ASCs outside clinical trials without infringing on clinical freedoms or stifling innovation in clinical care. Some countries have already activated these mechanisms by sanctioning offending practitioners. In 2010, the British General Medical Council deregistered Dr Robert Trossel for unjustifiably administering an allogeneic cellular preparation (also found to contain bovine neural cells) to patients affected by multiple sclerosis at a clinic in Rotterdam. The Singapore

Medical Council has previously sanctioned four of its practitioners for offering various stem cell products without evidence of efficacy, but has since withdrawn two following an appeal. Florida's Board of Medicine has also revoked the license of Dr Zannos Grekos following the death of two patients following or during procedures intended for the delivery of autologous stem cells, which is now under appeal. These enforcement actions may not have deterred physicians from routinely offering unproven stem cell interventions outside clinical trials, at least not the US, although they are unlikely to have harmed innovative practice in any of these countries.

While these actions are commendable, additional measures clearly need to be taken over and above the sanctioning and deregistration of individual practitioners. For instance, better guidance is needed to clarify the circumstances in which autologous ASCs may be administered to patients before sufficient evidence of safety and efficacy has been established in clinical trials. The Texas Medical Board (2012) has introduced rules on the investigational use of human stem cells that appears to provide an alternative to the IND pathway by allowing physicians to seek IRB approval to prescribe agents not approved by the FDA in their practice. These guidelines have been the subject of extensive criticism, principally because they appear to substitute formal regulatory oversight with IRB approval (Levine, 2012), even though federal manufacturing standards supersede state laws. The *Practice Notice* in Japan also attempts to provide guidance for physicians who use autologous cells in their practice by encouraging ethics approval.

Where regulators can take greater action is to enforce the existing laws that regulate the advertising of medicinal products. All five countries have tort laws in place for medical negligence and consumer protection legislation that restrict false advertising and the provision of misleading information in medical practice. Practitioners, healthcare providers and manufacturers who create websites and advertise the routine use of interventions with autologous ASCs that have not been established as an accepted standard of care, or provide misleading information about the effectiveness of such interventions, should be prosecuted under the relevant laws. These laws can be activated without infringing on the autonomy of patients or practitioners who use innovative biomedicines responsibly and in the best interests of those under their care.

Conclusion

Given our comparative analysis of regulatory frameworks in the five countries studied, it remains unclear why autologous ASCs are being prescribed outside clinical trials more often in Australia, Japan and the US, than in Singapore and the UK. Although we found technical differences in how key terms are defined within the regulations, and ambiguities that could be interpreted differently across jurisdictions, these do not sufficiently account for why the use of autologous ASC has proliferated in some countries and not others. All of these countries clearly regulate clinical practice with an emphasis on evidence-based medicine, while allowing clinicians to develop innovative care in a limited, responsible manner, and patients to access CTPs that lack the level of evidence necessary for market authorization or reimbursement from public and private health insurers. While this approach may support

research and in some cases work in the interests of patient autonomy and access to care, it also creates structural weaknesses that may be exploited by commercial interests who either willfully misinterpret ambiguous definitions in the regulation of drug research or ignore them altogether.

In discouraging the exploitation of vulnerable patient populations while still allowing scientific and clinical innovation, relevant authorities should work together in standardizing the terminology and scientific processes used to define and classify CTPs as minimal risk and exclude them from regulation. The difficulties seen in harmonizing regulations across EU countries, however, suggest that standardization across diverse jurisdictions will be even more challenging, as key terms may still be interpreted and acted upon differently according to national interests and the local needs of patients. Scientific definitions and evaluations of risk are also contestable. Thus, the solution is unlikely to come from simply clarifying and standardizing nomenclature, although this could help regulators improve the transparency of drug designations.

In our opinion, the structural weaknesses described above manifest in the separation of research regulation from clinical governance, and solutions must address how novel therapeutics are introduced into the practice of medicine. Safety alone is not sufficient to justify routine clinical use of ASCs as even low risk products should show compelling evidence of efficacy before they are introduced into healthcare systems and accepted as the standard of care. While we can activate and enforce existing consumer protection laws and prohibitions on false and misleading advertising in medical practice, these are *post hoc*

mechanisms where the burden is placed on adequately-resourced patients and authorities to demonstrate evidence of wrongdoing; and in taking such action, plaintiffs may potentially be exposed to counter-suits for libel. Medical authorities may also take a more proactive role in sanctioning practitioners whose conduct falls outside accepted professional standards and provide better guidance for those who want to prescribe innovative biomedicines *responsibly* before evidence of efficacy has been established in clinical trials. However, the impetus of these actions remains with the medical profession, and the lack of sanctions against practitioners who continue to prescribe autologous ASCs without evidence of their efficacy suggests that the self-regulatory model of clinical governance is becoming outdated. New models are needed to oversee the introduction of novel CTPs into clinical contexts in ways that acknowledge and allow for scientific uncertainties while enabling patient access to novel treatments and ensuring that rigorous and responsible research is unimpeded by commercial interests.

Web Resources

URL access to legal citations:

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Texas Medical Board (2012). Texas Administrative Code, Title 22, Part 9.

Tables

Table 1: Agencies that regulate medicinal drug products.

Jurisdiction	Regulatory Agency	Jurisdictional Laws & Regulations
United States	Food and Drug Administration (FDA)	Public Health Services Act (42 USC §§262, 264, 271) Code of Federal Regulations (21 CFR §1271)
Japan	Ministry of Health, Labour and Welfare (MHLW)	Medical Practitioners Law, Law No. 201 of 1948 Practice Notice: Conducting Regenerative and Cellular Medicine Using Autologous Cells and Tissues at Medical Institutions (2010) Regenerative Medicine Law (draft)
	Pharmaceuticals & Medical Device Agency (PMDA)	Pharmaceutical Affairs Law, Law No. 145 of 1960,as amended
Australia	Therapeutic Goods Administration (TGA)	Therapeutic Goods Act 1989 and Regulations 1990 (Cth) Australian Regulatory Guidelines for Biologicals
Singapore	Health Sciences Authority (HSA)	Medicines Act (1975, revised 1985) Medicines (Clinical Trials) Regulations (1978, revised 2000) Health Products Act (2007)
United Kingdom	Medicines and Healthcare Products Regulatory Agency (MHRA)	The Medicines Act (1968) Human Medicines Regulations 2012 (SI 2012/1916).
	European Medicines Agency (EMA)	Advanced Therapy Medicinal Products Regulation (EC No 1394/2007) and Directive (2001/83/EC)