Harmonizing standards for producing clinical-grade therapies from pluripotent stem cells

To the Editor:

Generating clinical-grade cells from pluripotent stem cells (PSCs) for use in patients is not simply a matter of complying with current good manufacturing practices (cGMPs) and chemistry and manufacturing controls (CMCs). A range of other issues demand careful attention, including accessing tissue in an ethical manner and adhering to the varied rules and regulations of specific local and national jurisdictions. The current patchwork of practices represents a major hindrance to progress in regenerative medicine. We propose the establishment of an international body tasked with developing, evaluating and harmonizing the technical, ethical, legal and regulatory frameworks that govern the production of therapies based on PSCs.

All PSC-based therapies involve the *in vitro* conversion of embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs) into differentiated cells that migrate, integrate, survive and function therapeutically in patients[1,2]. These therapies will be administered by different routes, alone or in combination with biologic or synthetic materials, for a variety of indications, and will require different final-product formulations. Although no PSC-based therapy has yet been approved, at least six or seven groups have commenced or are planning early-stage clinical trials.

Unlike somatic cells, PSCs are immortal and have the potential to make any differentiated cell type. These differences have important consequences at all stages of clinical translation, manufacture and commercialization, including requirements for shipping, tracking and identity specifications. Therapies based on somatic cells (including multipotent stem cells or other nonpluripotent cell types) involve collecting cells from a particular donor followed by limited growing, testing, storing and banking of the cells. Manufacture of somatic cell–based therapies involves myriad challenges, including compliance with cGMP and CMC regulations, scale-up and scale-out, and appropriate in-process testing and sterility and potency assays. But therapies based on PSCs bring additional layers of complexity. The cells must undergo extensive expansion and long differentiation procedures to generate appropriate phenotypes while eliminating unwanted phenotypes, including residual pluripotent cells[3,4]. The use of iPSCs as an autologous product that may be genetically modified raises further issues related to small lot sizes and lack of a master cell bank as in allogeneic therapies. The unique challenges associated with PSC-based therapies are summarized in **Table 1**.

In our view, the manufacturing challenges specific to these therapies mean that existing cGMP and CMC regulations conceived for somatic-cell therapies will have to be modified[5,6]. For example, use of iPSCs may require special guidance with respect to tumorigenicity, genetic integrity, release assays and sterility/aseptic processes. Confusion will arise if existing guidelines are inappropriately adapted or protocols are inadequately generalized to all cell types[7–9].

It is important to recognize that producing a clinical-grade, PSC-based therapy involves more than complying with cGMP and CMC manufacturing standards. Additional issues that must be considered include regulations on sourcing of donor tissue, ethical guidelines, intellectual-property law and data sharing. **Figure 1** outlines the hurdles that arise at different stages of product development.

Many of the issues summarized in **Figure 1** remain unresolved. For example, in manufacturing, new reference or control material is needed to generate convincing data on in-process testing, lot-to-lot variability and release assays. Guidelines for tissue collection, ownership and payment for PSC generation are in flux[10]. Equally important, questions regarding consent for the hundreds of thousands of existing samples that could be used as a source of iPSCs must be addressed. More generally, there are uncertainties in how to extend the regulations and standards of institutional review boards, HIPPA (Health Insurance Portability and Privacy Act) and OHRP (Office for Human Research Protection) to PSC-based therapies[10,11]. This new class of therapy may also require new interpretations of ethical guidelines[12], patent law[13,14] and the unique property-rights issues that arise for cells that can make gametes[15].

Table 1 Differences between PSCs and somatic cells

PSCs	All other cells	Comment
Broader developmental potential and multiple uses	Adult stem cells have more limited developmental potential and for most tissues and organs are not present in sufficient number to be clinically useful	Raises manufacturing issues related to tracing, tracking and storage
		Raises issues related to privacy and guaranteeing confidentiality
Spontaneously immortal and don't undergo senescence	Immortalization can be achieved but often changes phenotype and karyotype	Raises issues related to consent, distribution, patent ownership and reach-through to downstream progeny
Mutations can be repaired by engineering	Although mutations can be repaired in adult cells, current technology is inefficient and does not allow clonal isolation while retaining sufficient expansion capability for clinical utility	Widens the utility of the cells and adds a layer of regulations related to gene therapy
		Raises issues of negotiating with multiple patent holders of multiple technologies
Can make gametes	Limited reports on generation of gamete precursors	Raises ethical issues and changes material ownership rules
Can make living organisms and chimeras	Most studies suggest that no other cell type has this potential	Raises ethical issues, changes material ownership rules and raises issues related to insertion of cells into animals
Can make neural tissue	Most adult cells and cell lines cannot create neural tissue in sufficient numbers to raise concerns	Raises issues of selfhood and human animal transplants
iPSCs are suitable for autologous therapy	Autologous therapy only possible in limited instances	Cost of autologous therapy raises issues of access and fairness

Complicating matters further, all of these regulations differ between different national or regional authorities, leading to manufacturing inefficiencies, regulatory incompatibilities and ethical dilemmas that obstruct progress in the field. For example, whether a PSC line can be used for therapy varies in different countries depending on when consent is obtained, whether consent allows research or clinical use of samples, and what withdrawal of consent means. There are differences in the rules covering the use of serum; a serum-exposed product manufactured in the United Kingdom cannot be imported into the United States. ESC lines cannot be patented in Europe or in Korea but can be patented in the United States. Human genetic material cannot be shipped out of India, and it is very difficult to obtain ESCs from Japan. Conflicting regulations limit the use of banked PSC lines to particular countries or patients, or, in many cases, to no one. PSC-based therapies are being developed to treat a broad range of diseases, and the regenerative medicine community must strive to provide the therapies efficiently in as many countries as possible.

Ongoing efforts by regulators and others to address these issues, while commendable, lack coordination. We urge all stakeholders to work together to build a consensus strategy that enables harmonization and appropriate prioritization of tasks. This letter, signed by members of several public and private organizations in the field, represents a first step toward building such a consensus. We propose a set of issues that should be addressed, divided into those that are within (**Box 1**) and those that are outside (**Box 2**) the purview of regulators. We are optimistic that a concerted effort by all parties—academic investigators, the biotech and pharmaceutical industries, professional societies and associations, and regulators—would succeed in establishing an effective process to ease the development pathway of PSC-based therapies.

The most productive route may be the formation of an international, autonomous body, similar to bone marrow donor registry programs or blood bank

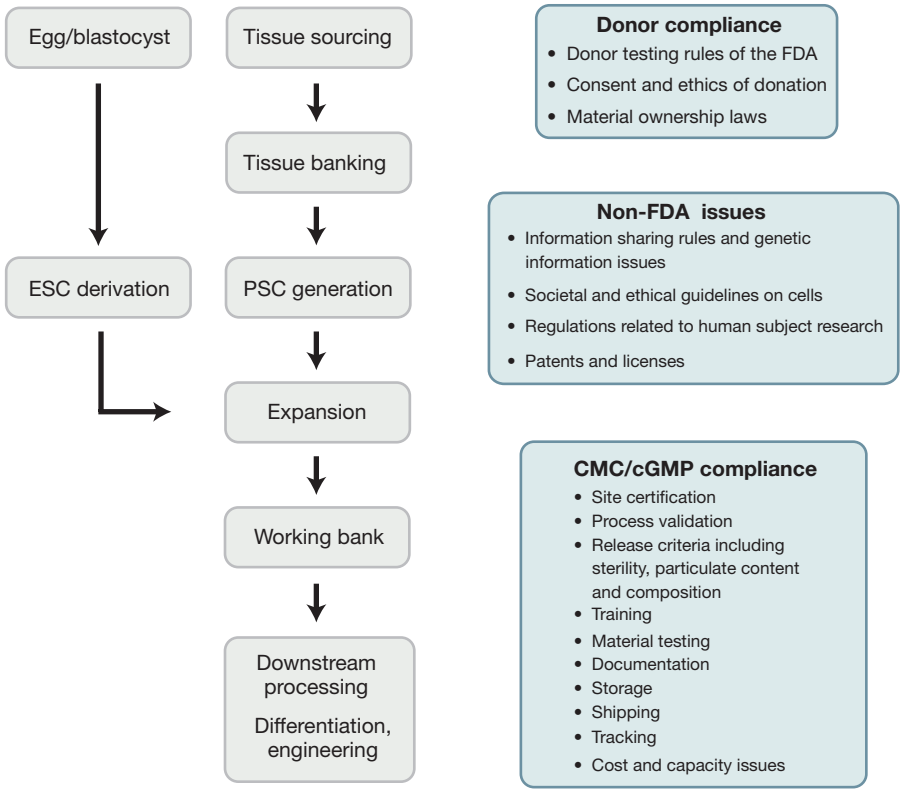

Figure 1 The manufacturing process for PSC-based therapies. Multiple regulatory, ethical and business issues must be considered (right). The figure excludes issues related to evaluation of cell therapies in clinical trials.

Box 1 Recommendations to regulatory authorities

The following ethical, regulatory, policy and patent issues should be addressed to accelerate clinical translation of PSC-based therapies. Issues that are also relevant to somatic-cell therapies are indicated with an asterisk.

Ethics
- Derivation, compensation and sourcing from deceased individuals
- Ethical criteria for including lines in the US NIH Human Embryonic Stem Cell Registry (US specific)
- Transplants into animals, including stage of development

Regulations
- ESC and donor consent
- Human subject research and information firewalls as related to immortal cells
- Chimera experiments as related to germ line and central nervous system competence
- Shipping, tracking and prion protein testing*

Procedure and policy
- Privacy and confidentiality issues associated with widespread distribution
- Ownership of donated tissue
- Donations and payments for commercial use
- Therapy, testing and quality control and release criteria for autologous use*

Patents
- Worldwide consensus on patentability
- Definition of patentability, taking into account recent patent law rulings
- Reach-through of patents to differentiated cells derived from pluripotent cells
- Reach-through of process patents
- Challenge process for overly broad patents*
- Identification of patents deemed essential to the field to establish rules for access, similar to what has been done with hardware and chip design patents

Box 2 Recommendations to other stakeholders

The following issues related to PSC-based therapies would benefit from a coordinated approach led by an appropriate body. Addressing these issues does not require new rules and regulations but involves obtaining consensus or establishing resources or infrastructure, such as a database, an agreement on standards or reference material. Many such efforts have been pursued by professional societies and public-private alliances, but a global, coordinated approach has been lacking.

- Consent and information-sharing guidelines
- A shared model for human leukocyte antigen–typed cell banking
- A process to make cGMP-compliant differentiated cells available for evaluation
- Standards for cGMP manufacture and cross-sharing agreements
- Issues related to international shipping of human material
- Searchable database of lines and uniform nomenclature
- Reference or control lines, including reporter lines, for preclinical studies
- Database of associated patient information
- Cost-reduction strategies for manufacturing
- A precompetitive model or a patent commons model for investigators developing therapies

associations and supported by national governments and international societies, including the International Society for Stem Cell Research and the International Society for Cell Therapy. Such a body could hold regular meetings and provide specific recommendations to regulators on issues including consent, databases and cell registries, and standards for cell manufacture, nomenclature, shipping, tracking and cell identification.

In all likelihood, the number of investigational new drug applications for PSC-based therapies will continue to increase, given recent support of this field by funding agencies and work on setting up human leukocyte antigen–typed, clinically compliant, stem cell banks[16]. We hope that this letter will spur an international initiative aimed at standardizing the contradictory thicket of existing regulations and proposing new regulations to accelerate translation of PSC-based therapies to patients[17].

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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