Enabling Consistency in Pluripotent Stem Cell-Derived Products for Research and Development and Clinical Applications Through Material Standards

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SUMMARY

There is a need for physical standards (reference materials) to ensure both reproducibility and consistency in the production of somatic cell types from human pluripotent stem cell (hPSC) sources. We have outlined the need for reference materials (RMs) in relation to the unique properties and concerns surrounding hPSC-derived products and suggest in-house approaches to RM generation relevant to basic research, drug screening, and therapeutic applications. hPSCs have an unparalleled potential as a source of somatic cells for drug screening, disease modeling, and therapeutic application. Undefined variation and product variability after differentiation to the lineage or cell type of interest impede efficient translation and can obscure the evaluation of clinical safety and efficacy. Moreover, in the absence of a consistent population, data generated from in vitro studies could be unreliable and irreproducible. Efforts to devise approaches and tools that facilitate improved consistency of hPSC-derived products, both as development tools and therapeutic products, will aid translation. Standards exist in both written and physical form; however, because many unknown factors persist in the field, premature written standards could inhibit rather than promote innovation and translation. We focused on the derivation of physical standard RMs. We outline the need for RMs and assess the approaches to in-house RM generation for hPSC-derived products, a critical tool for the analysis and control of product variation that can be applied by researchers and developers. We then explore potential routes for the generation of RMs, including both cellular and noncellular materials and novel methods that might provide valuable tools to measure and account for variation. Multiparametric techniques to identify "signatures" for therapeutically relevant cell types, such as neurons and cardiomyocytes that can be derived from hPSCs, would be of significant utility, although physical RMs will be required for clinical purposes. STEM CELLS TRANSLATIONAL MEDICINE 2015;4:217–223

INTRODUCTION

Human pluripotent stem cell (hPSC) technologies have a unique potential to address the increasing burden of unmet clinical need for many intractable diseases. However, a grasp of the fundamental biology, which is necessary to ensure invariant and reproducible, safe and effective cellular products from batch-to-batch and patient-to-patient, has eluded our reach. The field generally lacks standards that will enable scalable, automated manufacturing to build regulatory confidence and meet clinical needs.

Written standards exist in a vast range of industries, enabling dialogue between stakeholders via a common set of "rules" or "guidelines." Typically developed through consensus that emerges through an incremental process of discussion and revision among experts, standards can establish specifications, set minimum requirements, and provide a route by which valid comparisons can be made. Standards can also serve to protect the integrity of manufacturers, stimulate consumer confidence, and facilitate the uptake of new technologies into the market [1, 2]. Importantly, physical standards or reference materials used for specific comparative purposes are needed to validate and provide a benchmark for assessments of product or analytical tools.

Outlining the need for routes to generating both developer-specific and, where appropriate, consensus physical (material) standards for stem cell translation has value for two primary reasons. First, physical standards will support and enable improved reproducibility and product consistency in research. Currently, the field, and biomedical research in general, suffers from issues of irreproducibility [3, 4], which impede progress and effective collaboration and could damage the public perception of stem cell research. Second, commercial and translational benefits will result from incorporating standardization principles early in research and development by building a base for quality assessment to prevent undue delays throughout clinical trials because of deficiencies in the necessary tools and data to meet regulatory requirements. Therefore, approaches for the derivation of standards and, especially, physical (material) standards could benefit early-stage researchers conducting preclinical phase investigation, as well as those engaged further along the translation pathway. However, it is vital to strike the proper balance to ensure that the benefits of standardization are not achieved at the expense of hindering innovation. In the present report, we are not trying to identify the preferred PSC line to generate clinical products nor a specification for the optimal cell type. Instead, we have focused on the need and possible mechanisms by which physical standards, reference materials (RMs), can be produced to analyze and thereby facilitate the consistent and reproducible generation of products from hPSCs. Because consensus (international) RMs might have limited application and would be more challenging to achieve, we have focused on in-house developer-specific RMs that can be generated by research laboratories and companies alike that are engaged in preclinical research and that can be applied in clinical trials and beyond to meet regulatory expectations. These principles and approaches also have application in drug screening and toxicology studies that use PSC-derived somatic cells with underlying expectations for reproducibility and consistency.

CLINICAL POTENTIAL OF PSC-DERIVED PRODUCTS

The utility of hPSCs in disease modeling is beginning to be demonstrated, and some of these models are now finding application as drug screening tools (reviewed in [5–8]). However, it is the application of PSCs as a cell source for therapeutic intervention that still garners the greatest enthusiasm within a healthcare context. To date, embryonic stem cell (ESC)-derived products have entered a limited number of clinical trials, pioneered by Geron Corporation (Menlo Park, CA, http://www.geron.com; assets now owned by Asterias Biotherapeutics) and more recently Advanced Cell Technology, Inc. (Santa Monica, CA, http://www.advancedcell.com), with a Pfizer/University College London trial that began in 2014 [8, 9]. Although Geron did not complete its trial of ESC-derived oligodendrocyte precursors for acute spinal cord injury owing to internal competing fund allocations, it pioneered a regulatory path and demonstrated the data requirement for testing PSC-derived products in humans [9]. This exercise proved educational, not only for the private sector, but also for the regulators themselves, who, until that time, had had no experience evaluating the safety of hPSC-derived products in actual patients.

Standards for hPSCs in their undifferentiated state are important for cell banking, both to demonstrate comparability and to show that cell lines are stable over time [10, 11]. A number of engaging perspectives on standards for hPSCs have been reported [10, 12–14]. However, because hPSCs in their undifferentiated state will not be the final product delivered to research subjects or patients, the standards should extend to validating early-stage translational research and the manufacture and scale-up process by which large numbers of somatic cells are derived from hPSCs. Just as with any cell therapy, owing to the unique nature of each product, written standards will have limited utility for hPSC-derived products. Instead, material standards, generated on a case-by-case basis, will be required to validate the process, method, and product consistency. Although such material standards will be the responsibility of the developer and will vary in accordance with the particular developer's technology, product, and target indication, a clearer understanding of the needs, requirements, and potential approaches by which these materials standards could be produced will benefit academic researchers and industry alike.

CHALLENGES OF HPSC TRANSLATION

The application of hPSC-derived products in a clinical setting has been challenged by the numerous inherent and unique barriers to translation, including scalability and manufacturability, and a variety of regulatory challenges:

- Phenotypic and genetic instability
- Capacity to generate adult phenotypes
- Cost of cell culture processes
- Clarity of protection for intellectual property
- Differentiation efficiencies and time scales
- Tumorigenicity risks
- Immunological considerations
- Paucity regulatory and sponsor familiarity
- Limited positive cell therapy outcomes to date
- Each product must be considered by regulatory authorities on a case-by-case basis

hPSCs are highly reactive to their external environment. They can undergo significant changes in response to different culture conditions, to extended time in culture, and after cryopreservation

[15–17]. Stability is also a key issue, both genetic stability and the physiological stability of hPSC-derived products. Compared with cells harvested from adult donors, hPSC-derived populations might have an increased propensity for continued proliferation, differentiation, and/or maturation. This was exemplified by the increased frequency of cyst formation from the ESC-derived oligodendrocyte precursor cell population in Geron's preclinical animal studies, which resulted in the Food and Drug Administration (FDA) placing the trial on hold. This issue was ultimately resolved by an additional level of cell selection [18]. Furthermore, hPSCs and their differentiated progeny have been demonstrated to be highly heterogeneous at the population level, with differentiation protocols asynchronously generating a variety of cell types [19]. Researchers are focusing on the generation of homogeneous-differentiated populations from hPSCs that would be amenable to clinical demands. However, it has been argued that mixed populations might be preferable to a single cell type in some cases, if the survival or efficacy of administered cells will be enhanced by the presence of interacting cell types. It will be more challenging to characterize and control the consistency and quality of mixed populations, acknowledging that the level of heterogeneity in cell products will always exceed that of traditional small molecules. These inherent characteristics and current methodologies all create significant challenges for the development of RMs for hPSC-derived products.

The challenges to the translation of hPSC-derived products are as follows:

STANDARDS AND REFERENCE MATERIALS

Standards fall into two main categories, written and physical (material), which must be clearly distinguished (Fig. 1). Written standards include codes of practice, standard operating procedures, agreed terminology, guidelines, and pharmacopoeia methods. Pharmacopoeia, particularly relevant to this discussion, are a series of monographs and general chapters for active substances that outline the minimum requirements, describing the identity and permissible levels of impurities, in addition to appropriate methods to define purity and potency, with accompanying expected ranges (USP, 2011). Pharmacopoeia can require the use of consensus physical (material) standards, which currently only exist for small molecules and a limited number of biologics. The single example of a cell therapy monograph is currently being developed by the USP Convention for sipuleucel-T (Provenge; Dendreon, Seattle, WA, http://www.dendreon.com), a T-cell therapy for advanced prostate cancer that has been authorized by the FDA, although approval of the monograph could encounter challenges and application might be limited (USP, 2013). A variety of local and regional organizations are concerned with the publication of pharmacopoeia and/or the production of physical reference standards (Table 1). In addition, organizations such as the World Health Organization and the Joint Committee for Traceability in Laboratory Medicine—the latter in the context of laboratory medicine and in vitro diagnostics, can lead and coordinate in the establishment of higher order international RM [20].

RMs are highly characterized physical materials used with analytical methods for a specific comparison purpose and are a global regulatory expectation [21–24]. Physical (material) standards can be subsegmented into certified (consensus) and in-house (developer-specific) materials (Fig. 1). Although certified RMs are
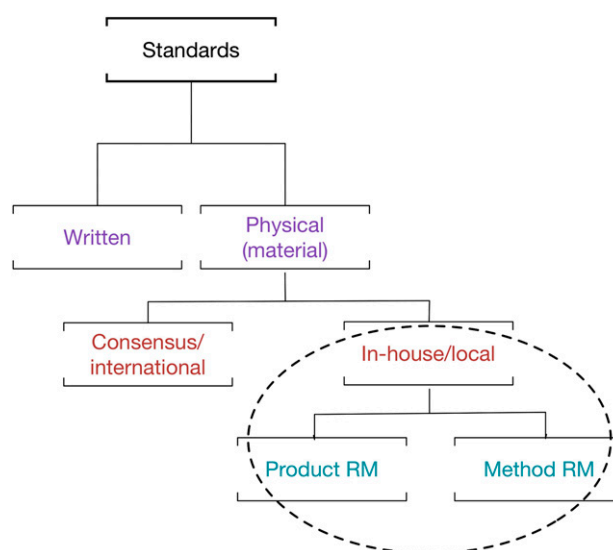

Figure 1. Overview of standards. Standards are a set of guidelines, rules, or requirements, typically set by a regulatory body or product manufacturer. They ensure that either during manufacture of a product or in the final product, some aspect, such as safety, performance, or quality, is consistent. Standards are either written, in the form of guidance, standard operating procedures, and pharmacopoeia, or they are physical (material). Physical standards are characterized materials used as a benchmark against which to compare attributes of a product and ensure consistency. They can be agreed on across organizations and countries (consensus) or can be developer-specific and local (in-house) (i.e., the standards are only adopted within the organization in question). These in-house material standards, called RMs, are the focus of our review and can be further divided into a product RM, which is a representative batch of the product, or a method (measurement) RM, which provides a reference for analytical measurements. Abbreviation: RM, reference material.

available for many biological substances, they have not yet been produced for cell therapies. The National Institute for Biological Standards and Control (NIBSC) has produced a RM of untouched (enrichment using negative selection techniques to prevent activation) $CD4^+$ cell-certified RM, intended for use in clinical diagnostics. This standard comprises fixed peripheral blood mononucleated cells prelabeled with a CD4 antibody conjugated to fluorescein isothiocyanate (NIBSC, SS-222); this approach could have some relevance for cell therapies, as discussed below [25]. Certified (consensus) RMs might have application when applied to specific characterization methodologies but are highly unlikely to have a broad application, especially considering the need for case-by-case development of cell therapies such as hPSC-derived products. Therefore, we have focused exclusively on in-house (developer-specific) RMs. There are two main categories of in-house, developer-specific RMs, "product" and "method" (Fig. 1).

POTENTIAL APPROACHES TO DEVELOPING REFERENCE MATERIALS FOR hPSC-DERIVED PRODUCTS

The aim of the present discussion is to support the development of approaches and assays that will facilitate consistency and comparability in the production of differentiated cell types, such as cardiomyocytes, neurons, and T cells from hPSCs, or "hPSC-derived products." Batch-to-batch variation, if not assessed and controlled, will affect the quality of clinical hPSC-derived products. Moreover,

Table 1. Organizations concerned with the generation and/or oversight of reference materials, including a list of major organizations that play a role in the production, guidance, and/or directives concerning reference materials for small molecule drugs and biologics

Organization	Region	Description	Web address
National Institute for Biological Standards and Control	United Kingdom	The leading WHO International Laboratory for Standards is responsible for >90% of global WHO standards	http://www.nibsc.org
USP Convention	US	The official organization that sets standards and generates reference materials implemented by the FDA as law in the United States, used globally in >140 countries	http://www.usp.org/about-usp
World Health Organization	International	Publishes the International Pharmacopoeia, which aims to harmonize global pharmaceutical standards and administers the establishment of international reference materials	http://www.who.int/medicines/ publications/pharmacopoeia/ overview/en/
European Directorate for the Quality of Medicines & Healthcare	Europe	Responsible for the European Pharmacopoeia commission, the evaluation of manufacturer's quality dossiers for certification, and market surveillance program	http://www.edqm.eu/en/ edqm-homepage-628.html
Pharmaceutical and Medical Device Regulatory Science Society of Japan	Japan	Produces and distributes Japanese Pharmacopoeia Reference Standards as prescribed in the Japanese Pharmacopoeia (published by Pharmaceuticals and Medical Devices Agency)	http://www.pmrj.jp/hyojun/html/ frm031.php?lang=e

Abbreviations: FDA, U.S. Food and Drug Administration; WHO, World Health Organization

approaches that enable the consistent production of differentiated cells will also be of significant benefit to drug and toxicity screening. The potential causes of variation in the production of somatic cells from hPSCs are numerous. "Products," such as cardiomyocytes, are generated from hPSCs by a highly dynamic differentiation process that might use a variety of methods [26], typically occurring via a number of stages. Even when considering the production of one specific product, from one hPSC line, using a single method, it is inevitable that the final product will demonstrate variability among the individual batches. This variability will arise in the form of variable levels of heterogeneity and "purity" of cell types and in inconsistencies in the differentiation and/or maturation stage of the product. Additionally, both genomic and phenotypic stability could demonstrate variation. We have detailed approaches to RM generation that might mitigate the current inconsistency and irreproducibility concerns.

An overview of the possible approaches to establish RMs for hPSC-derived products identified two main categories: those that use living, cellular RMs, either as product or method RMs, and those involving nonliving, noncellular materials, such as beads or DNA or RNA samples, as method RMs (Table 2).

Product Reference Material Approaches

"Product" RMs should be representative of the product and are used to validate comparability assessments throughout the product's lifecycle, including process change and optimization, and to detect process drift (Fig. 2A). Individual RMs will be designed to assist in the assessment of the product identity or its biological potency, and the respective purpose for the RMs must be clear at the outset.

The typical approach, which is common practice in the pharmaceutical industry, is to generate primary and secondary RMs that are samples of the product batch generated for preclinical and then pivotal studies. Secondary RMs are the working samples used as a comparator in the relevant tests. Once the samples have been depleted, the secondary RM is generated from another

batch and, through rigorous characterization, determined to be sufficiently comparable to the primary RM via a direct comparison. Ideally, the quantity of primary RM would be sufficient to last for the lifecycle of the product (in some cases, more than 20 years). However, and as discussed below, limitations could be present that would preclude this period of coverage.

A second potential method to product RM generation involves a "pooling" approach, in which cells from a number of different batches are pooled. If RMs are generated using a pooling approach, the differences due to heterogeneity within the product will be averaged out, providing a broad-ranging background against which measurements can be assessed. This could be beneficial in a number of circumstances.

In a limited number of cases, biologically equivalent cellular populations might be suitable product RMs. For example, if $CD4^+$ T lymphocytes are derived from hPSC lines, $CD4^+$ T lymphocytes harvested from healthy donors might be suitable as a product RM or, potentially, as a method RM for a limited number of assays. This approach might only be appropriate for a limited number of cell types that can be obtained from healthy donors without causing a detrimental effect. Although this approach might have potential utility, it must be acknowledged that the heterogeneity in the "biologically equivalent" RMs would need to be analyzed and accounted for.

The considerations of whether these approaches would be suitable, in addition to the critical criteria of relevance to the product, include stability, feasibility, and cost. Stability will need to be monitored over time and stability profiles determined so that new RM can be prepared before expiry. Because the batch sizes for hPSC-derived products are expected to be smaller than typically seen with small molecules and even biologics, the amount of product that can be stored as RM will also be limited. The practicalities of RM quantity requirements will vary and should be mapped out and planned for by developers. An additional challenge for approaches that rely on cellular RM is that the cell banks of differentiated products will need to be cryopreserved, which will affect

Table 2. Potential approaches to generating reference materials for PSC-derived products

RM category	RM description	Type	Explanation
Product	Primary/ secondary	Cellular	Generated as per product. Primary and secondary RMs. Secondary RM is used as the working material that, when depleted, is replaced with product from a new batch and qualified against the primary RM.
Product	Pooled	Cellular	Generated as per product. RMs are produced from a pooled bank of cells. A potential benefit is that variability is averaged across the population.
Product/ method	Biological equivalent	Cellular	For a limited number of cell types that can be harvested from donors noninvasively (e.g., from blood), biological equivalent cell populations can be used as a RM (e.g., expression of CD4 levels on peripheral blood T cells and on PSC-derived T cells).
Method	Cell lines	Cellular	Cells lines could have application in a number of characterization assays.
Method	Noncellular	Noncellular	Samples such as fixed cells for cell surface marker staining, DNA samples for sequencing or genotyping, and RNA for expression profiling.
Not a physical RM	"Virtual"	Noncellular	Use of transcriptome, proteome, phosphoproteome, or epigenetic mapping to generate a complex data set that, when computational algorithms are applied, identifies a product "signature" (e.g., concept from PluriTest, PSC scorecard) (data from Müller et al. [33], 2011; Bock et al. [34], 2011).

In-house RM for hPSC-derived products will enable the analysis and qualification of consistency and promote reproducibility. Product RMs are used to ensure that a product batch is representative of an intended product and to identify process drift. Method RMs are used to validate data derived from specific assays, define assay acceptance criteria, and as a tool to detect method drift.
Abbreviations: PSC, pluripotent stem cell; RM, reference material.

not only viability, but also, potentially, functional parameters. This will become an issue if the product is to be used "fresh" but is less of a concern if the product will be cryopreserved as a part of the production process.

Method Reference Material Approaches

"Method" RMs are used to qualify, validate, and define the acceptance criteria for specific assays, to calibrate methods and equipment, and to identify method drift over time (Fig. 2B).

Cell lines could be valuable method RMs in some settings. An example of such an approach is the use of embryonal carcinoma line 2102Ep, which has a good stability profile in culture. This cell line has demonstrated utility in flow cytometry assays for the characterization of a range of hESCs by the International Stem Cell Initiative [27], despite a number of reported biological differences between hESCs and the embryonal carcinoma line [14, 28]. This approach might also be relevant for a number of differentiated cell types, if an appropriate cell line is available or can be produced. Immortalization of primary cells to generate stable cell lines will affect signaling pathways and some phenotypic characteristics; therefore, the suitability of cell lines as method RMs will depend on the application. It should also be acknowledged that the standardization, characterization, and qualification of cell lines as method RMs would require a considerable amount of workup and validation.

Noncellular (nonviable) method RMs could include fixed cells, beads, DNA/RNA samples, and reference cytokines. Fixed cells, most suitably from a product sample, can be used as a RM for assays that compare cell surface marker expression, such as the clinical application of the NIBSC CD4$^+$ T cell sample for HIV testing, and applications to assess heterogeneity/composition criteria [25]. However, the process of fixation changes the properties of the cell, which could negate its use as a method RM compared with the nonfixed product in some flow cytometry-based assays. Bead-based approaches have routinely been used for flow cytometry purposes, to both calibrate and establish baseline readings for cytometers and to apply compensation settings. However, bead-based approaches also have stability issues and would most likely need to be used in conjunction with a cellular method RM.

RM for molecular biology assays should be more readily achievable, because DNA and RNA samples, in the appropriate conditions, have demonstrated good stability profiles, are easily stored, and can be generated in large quantities relative to the amount of material required for any given assay. In most cases, method RMs for molecular biology assays would be produced from a sample of the product batch. One issue to be considered is the selection of suitable positive controls in assays such as reverse transcription polymerase chain reaction (RT-PCR). Semiquantitative measurements of gene expression are typically made in relation to the expression of "housekeeping genes." However, a number of studies have identified changes in the expression levels of these presumably stable genes in concordance with the differentiation status of hPSCs and other stem cell types; therefore, these would be an unsuitable baseline for these assays [29, 30]. Similarly, although microarray-based assays detect the relative levels of all transcripts in the genome, they do not identify alternatively spliced transcripts that might be critical for cellular function. RNA sequencing (RNAseq) is increasing in popularity and has the potential to identify splice variants and absolute amounts of transcripts. A challenge for an RNAseq approach, however, is the large variation in the results from different sequencing laboratories, a problem that must be solved by a normalization method before sequencing-based assays can be reliable—another example of the need for physical reference materials to enable comparability testing. Written standards that identify a consensus minimum requirement for quantitative RT-PCR and microarray assays have been described [31, 32].
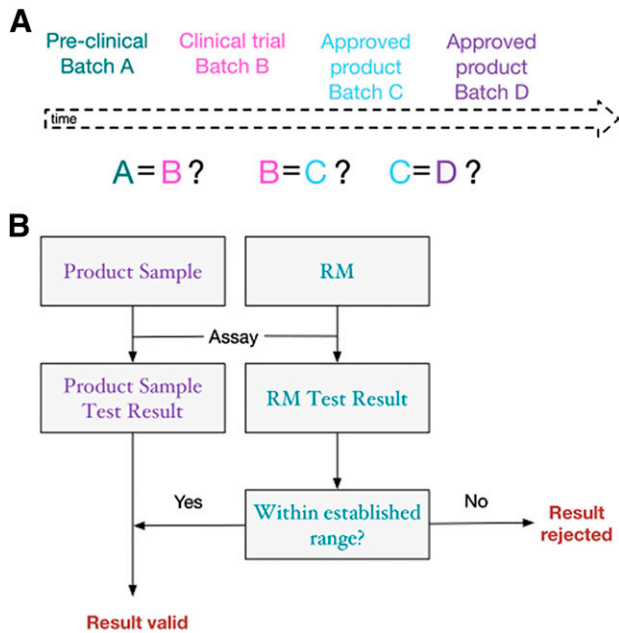
Figure 2. Reference materials are required to demonstrate product comparability over time (product RM) and to validate assay results (method RM). Product RMs are representative of some aspect of quality of a final product, and method RMs are used within assays to confirm the accuracy of the analysis of the product. They have multiple applications, two of which are depicted. **(A):** Product RMs are required to demonstrate that product drift does not occur. Product drift is the gradual change in a "product," potentially caused by a gradual change in a manufacturing process that can occur through iterations over time. Product RMs are a representative batch against which other batches can be compared to demonstrate consistency in characteristics such as identity and purity. For example, RMs generated with batch B, such as a sample of the iPSC batch, will be retained to use as a comparator with batch D to ensure that characteristics of batch D are within the expected range according to batch B. **(B):** Method RMs are needed to validate assay results alongside the product sample. For example, specific embryonic carcinoma (EC) lines, whose cell-surface antigens are well characterized, can be used as a quality control for flow cytometry assays in which human embryonal stem cells (hESCs) are also tested. If the score for the EC line is less than a certain predetermined threshold, the results of the accompanying assay of hESCs would not be included in additional analysis. Thus, the results will be representative of the actual hESCs and not of any problem in the assay, because the assay has been validated against a method RM with known characteristics. Abbreviation: RM, reference material.

Reference cytokines, such as those used to calibrate enzyme-linked immunosorbent assays (ELISAs), are available in some instances in the form of certified (international) RMs. However, although a reference cytokine can serve to define standard curves and therefore a link to a known concentration of that cytokine for an assay such as an ELISA, the reference cytokine is not a RM for the biological assay that results in cytokine release.

Although not a material standard, approaches that create product "signatures" from complex data sets and applied algorithms might have application in demonstrating comparability. Examples of such an approach that has been developed to assess (undifferentiated) iPSC populations by gene expression analysis include the hPSC Scorecard and PluriTest, either by genome-wide microarray (PluriTest [33]) or PCR analysis of a set of selected genes (Scorecard [34]), establishing a typical gene expression profile. Users analyze their samples via the same method (array or PCR) and compare their samples to the established standard

generated, in this case, from previous product batches. Such a comparison informs users regarding how similar their sample profile is to the expected profile. This approach might be suitable for the assessment of hPSC-derived products, in which a developer would perform a gene array (or other) analysis using multiple samples from different product batches. Then, using a similar approach to that of the PluriTest, an expression signature for the product would be generated with the identification of "acceptable" levels of variation. This data set could then be used as a "virtual" method RM when assessing the comparability of future product batches using the same method, in the context of a specific product. This approach would facilitate a move away from the inaccurate use of a limited set of cell surface markers, which are typically used to characterize and identify cell populations. Clearly, this approach would require validation and the application of a suitable RM.

The method RMs we have described will typically display greater stability profiles than product RMs owing to the inherent plasticity of living cells and their responsiveness to the environment. Feasibility factors, including the ability to generate sufficient batch sizes, will also be more amenable to method RM approaches, which should, in general, also carry lower costs. A rational mix of method RMs for different assays within the overall characterization process and robust product RMs will be required.

A final consideration is how the data will be made available and managed once the method and/or product RMs have been established. Given that discussion has focused on development of in-house RMs, external publication and management of data might not be required. However, rapid dissemination of open access and peer-reviewed publications for community wide access would be beneficial as a "formal" record and to catalyze multistakeholder dialogue. Eventually, it might be possible to develop online data repositories managed by experts in both research and regulation that would act as a centralized resource.

The approaches we have outlined are by no means exhaustive. Innovative thinking is required to envisage novel routes to RMs that would be appropriate to the unique characteristics of hPSC-derived products and cell-based therapies. It is clear that the different approaches will have varying levels of application, depending on the specific product and clinical application.

CONCLUSION

Uncontrolled variability and irreproducibility are key considerations for the translation of PSC-derived therapeutics and for the cell therapy field more broadly. We have outlined the need for RMs, discussed the potential challenges faced by hPSC-derived products, and identified possible approaches to alleviate consistency and reproducibility concerns in the production of hPSC-derived products. A range of cellular and noncellular approaches to product and method RM generation can be envisioned and have been described here, including relevant considerations. The ambition behind our report is for the research community and tool providers to engage around these requirements and existing industry and regulatory models and terminology, such that potential approaches will be assessed and incorporated into practice, as appropriate, and that novel thinking will lead to approaches that more satisfactorily fulfill the needs outlined.

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DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

R.W.B. is a compensated board member and has compensated shares and options in Celgene Corporation. B.R. is a compensated consultant for Boehringer-Ingelheim Pharmaceuticals and has compensated stock options in Pathfinder Cell Therapy. J.C.W. is an uncompensated cofounder of Stem Cell Theranostics; is an uncompensated consultant for Merck; has uncompensated research funding from the NIH, the California Institute for Regenerative Medicine, and Sanofi; and has uncompensated stock options in Stem Cell Theranostics. S.O. has compensated employment and uncompensated intellectual property rights with A*Star. D.A.B. is a stockholder in Translation Ventures Ltd. The other authors indicated no potential conflicts of interest.

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