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REVIEW

Manufacturing models permitting roll out/scale out of clinically led autologous cell therapies: regulatory and scientific challenges for comparability

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Abstract

Manufacturing of more-than-minimally manipulated autologous cell therapies presents a number of unique challenges driven by complex supply logistics and the need to scale out production to multiple manufacturing sites or near the patient within hospital settings. The existing regulatory structure in Europe and the United States imposes a requirement to establish and maintain comparability between sites. Under a single market authorization, this is likely to become an unsurmountable burden beyond two or three sites. Unless alternative manufacturing approaches can be found to bridge the regulatory challenge of comparability, realizing a sustainable and investable business model for affordable autologous cell therapy supply is likely to be extremely demanding. Without a proactive approach by the regulators to close this "translational gap," these products may not progress down the development pipeline, threatening patient accessibility to an increasing number of clinician-led autologous cellular therapies that are already demonstrating patient benefits. We propose three prospective manufacturing models for the scale out/roll out of more-than-minimally manipulated clinically led autologous cell therapy products and test their prospects for addressing the challenge of product comparability with a selected expert reference panel of US and UK thought leaders. This paper presents the perspectives and insights of the panel and identifies where operational, technological and scientific improvements should be prioritized. The main purpose of this report is to solicit feedback and seek input from key stakeholders active in the field of autologous cell therapy in establishing a consensus-based manufacturing approach that may permit the roll out of clinically led autologous cell therapies.

Key Words: *autologous cell therapy, comparability, GMP, manufacturing, point-of-care, scale-out*

Introduction

Recent analysis by Foley and Whitaker (1) has shown that an increasing number of clinician-led (i.e., clinical trials sponsored by an institution), predominantly autologous cellular therapies are demonstrating benefits to patients. Often involving complex routes of clinical intervention, these clinician-led therapies span those in which a degree of clinical adoption and proven efficacy already exists to those in which trials will be carried out under regulatory constraints more familiar with the regulatory route that industry-led cellular therapies must traverse (1).

Most companies seeking highly profitable business models work predominantly with scalable allogeneic therapies, following the traditional mass production biopharmaceutical manufacturing model as a route to market (1). Smaller-scale autologous therapies must follow alternative manufacturing and distribution approaches, dependent on the product (disease indication and prevalence), the method of preservation of the product and the fit with the systems in place at the final destination in the clinic (2). This may involve, for example, a central processing facility serving a number of clinical sites or a distributed model that requires localized processing within a hospital unit or manufacturing in-theatre or at the bedside through the use of closed or functionally closed automated processing systems.

The regulatory approach taken for specific autologous cell therapies is dictated by their intended

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clinical use, method of clinical delivery and manufacture. In some therapeutic cases, particularly in the orthopedic and cosmetic sectors, harvested cells are minimally manipulated (eg, by aseptic enrichment or separation techniques) and returned to the same patient. In most others, there is a requirement to expand the number of harvested cells in *in vitro* culture to generate a sufficient dose for therapeutic use. This expansion in culture, being considered by regulators to be more than minimal (or substantial) manipulation, raises considerable hurdles and challenges for both developers and regulators (3–6).

Manufacturing of more-than-minimally manipulated (MTMM) autologous cell-based therapies presents a number of specific challenges driven by complex supply logistics and the need to scale out (increasing the number of batches) production to multiple manufacturing sites or near to the patient within hospital settings. The existing regulatory structure in Europe and the United States sensibly imposes a requirement to establish and maintain comparability (demonstration of product equivalence) between sites.

At best, the assurance of comparability is achieved through a combination of *in vitro* studies, analytical testing and biological assays. Recently however, a consortium of stakeholders taking part in the Technology Strategy Board-funded Value Systems and Business Models project, known as "VALUE" (7,8), suggested that extensive safety testing of final cell product, while practical in the allogeneic setting, may not be feasible in the MTMM autologous setting. They concluded that because of restrictions related to small lot sizes, short shelf lives and the clinically limited time available for product and lot release testing it may not be possible to demonstrate comparability for additional manufacturing sites without costly and time-consuming confirmatory clinical qualification studies.

The cell therapy industry has experienced continued wrangling between regulators, lawmakers and practitioners and uncertainty as to the data required to establish quality, safety and efficacy of cell therapies (9–14), particularly with the International Society for Cell Therapy (ISCT) position on potency assays receiving recent attention (15). Against this backdrop, with point-of-care manufacturing not envisaged under current US and EU regulatory frameworks, with few MTMM autologous cell therapies on the market, for example, MACI (Genzyme), Provenge (Dendreon), ChondroCelect (Tigenix) and LaViv (Fibrocell Science), and with no precedent for a multi-site MTMM autologous cell therapy in Europe, it is clear that alternative cost-effective manufacturing approaches are required to permit the roll out of clinically led autologous cell therapies.

We propose three prospective manufacturing models for the scale out/roll out of MTMM, clinically led autologous cell therapy products, consider how they may be enabled and test their prospects for addressing the challenge of product comparability under the principles of the existing regulatory landscape. This paper presents the perspectives and insights of a small, selected expert reference panel of US and UK thought leaders from the industrial and regulatory community. It highlights the issues raised, identifies alternative manufacturing approaches, identifies where operational, technological and scientific improvements should be prioritized and where new enabling science is still required.

The regulatory challenge

Under the existing US and EU regulatory frameworks, cellular products that have been subject to more-than-minimal manipulation and/or do not carry out the same function in the recipient as the donor (non-homologous use) are broadly classified as either medicinal products (EU) or biologics (US), with relatively few regulatory distinctions made between autologous and allogeneic therapies and the characteristics that differentiate them (16,17).

In the autologous setting, the logistical hurdles associated with the clinically limited time available to transport harvested donor patient cells to the manufacturing or processing site and their return back to the clinical site for administration dictates both the manufacturing model (centralized versus distributed) and the clinical-site model (direct delivery versus clinical-site manipulation). This presents a number of ways of realizing the manufacturing/clinical supply process in multiple, distributed locations (Figure 1). The requirements for regulatory approval, Good Manufacturing Practice (GMP) and the level of validation relate, in part, to which sites are used for each element of the manufacturing and clinical process.

Manufacturers of autologous cell therapy products often introduce changes to manufacturing processes both during development and after market approval. Under the existing regulatory structure in Europe and the United States, when changes are made to a manufacturing process, the manufacturer is required to demonstrate comparability, that is, a demonstration of product equivalence before and after the change. This includes situations in which a second or reconfigured production line/unit, facility, location or supplier is brought on stream or when multiple sites of manufacture are introduced.

The scale out/transfer of manufacturing processes to multiple sites established before pivotal Phase III

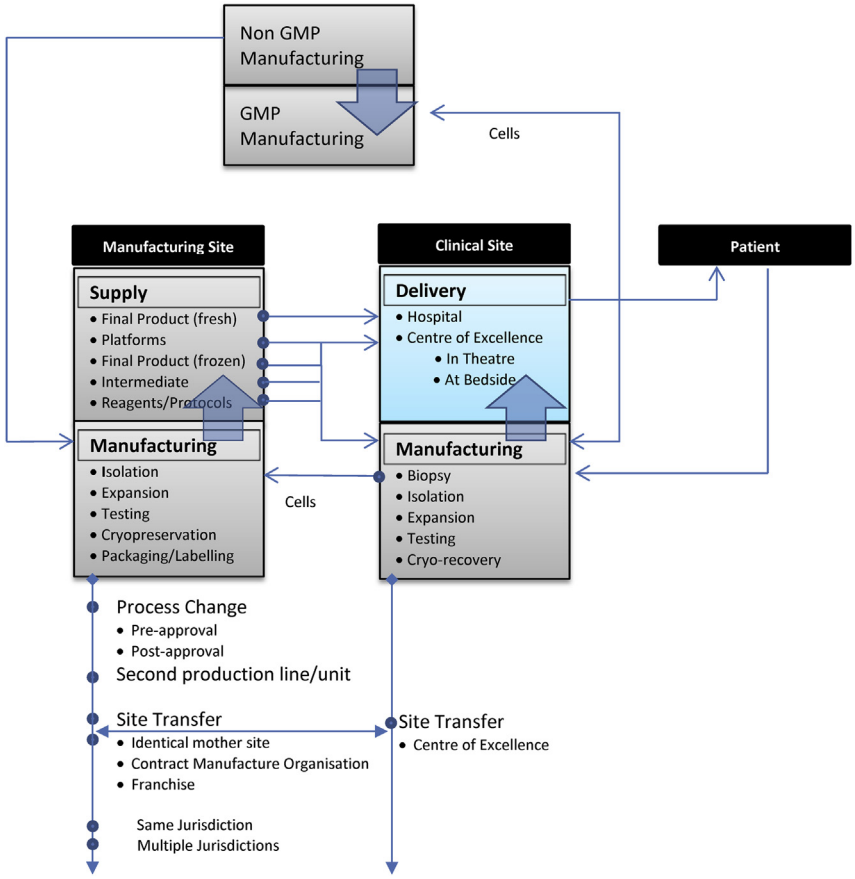

Figure 1. Alternative routes for manufacturing and clinical site process transfer and product delivery. The requirements for regulatory approval, GMP and the level of validation relate, in part, to which sites are used for each element of the manufacturing and clinical process, which in turn dictates how the manufacturing model may be implemented.

clinical trials (N model)[1] is probably achievable. Under a single market authorization, however, the roll out of locked-down processes to more than two or three sites (N+1 model) is likely to become an unsurmountable challenge, even within the same regulatory jurisdiction (7,18) (Figure 1). The challenge that this poses is no better illustrated than by Dendreon's conspicuous and costly issues with their multiple manufacturing site model and uptake of their autologous prostate cancer product (Provenge) (19).

[1]The following model convention is used to differentiate the origin and scale of the potential routes for manufacturing roll out to multiple sites: Transfer of a product/process from an academic or hospital laboratory to a regulated manufacturing site (0+1 model); transfer to one or more additional manufacturing/production line(s) or to a regulated manufacturing location(s) within the same jurisdiction, either before (N model) or after Phase III clinical trials (N+1 model); transfer of product/process to regulated manufacturing site(s) within different jurisdictions (N+M model), that is, a site in each of the major geographical markets, transfer to 20 or 30 processing sites (eg, sites in international Centers of Excellence for major clinical specialisms) or transfer to 100 to 500 processing machine platforms, that is, systems "within a GMP setting" or "GMP in-a-box" systems (an example of true process scalability).

The scientific challenge

Approaches to establishing the comparability of cell therapy products through manufacturing process changes are predicated on manufacturing reproducibility such that products are produced with consistent quality attribute profiles. The core of the scientific problem is to determine both the allowable variation in the product necessary to deliver quality, safety and efficacy and the achievable variation in the manufacturing process, taking account of variation of input or starting materials and variation in the patient population within the autologous setting. The challenge is doing this with the additional variation associated with multiple manufacturing sites while containing cost of goods and costs of validation. Persistent issues underpinning the challenge are associated with a poor understanding of the mechanism of action (MOA), poor definition of product characteristics that influence its quality, safety and efficacy and poor understanding of how changes or variation in the manufacturing process affect these characteristics.

Unless alternative manufacturing approaches can be found to bridge the regulatory and scientific

challenges of comparability, realizing a sustainable and investable business model for affordable autologous cell therapy supply is likely to be extremely demanding, even within a clinical setting. Without a proactive approach by the regulators to close this "translational gap," these products may not progress down the development pipeline. This threatens patient accessibility to an increasing number of clinician-led autologous cellular therapies that are already demonstrating benefits to patients (1).

Methods

The three manufacturing models proposed are premised on their ability to reduce the risk profile of the product and the manufacturing process. The models are specifically applied to the manufacture of MTMM autologous cells (defined as donor cells that are derived from the patient who is the sole recipient of the cell product, intended for use for the same [homologous] or different [non-homologous] essential function) and do not consider application to cells that are genetically modified or associated with a device.

Framed by the question, "How can developers provide transferable methods with sufficient evidence of comparability across multiple manufacturing sites without the need for extensive clinical qualification studies?" a selected expert reference panel of US and UK thought leaders was assembled to review and assess each of the manufacturing models. The panel comprised three prominent industrialists active within the Regenerative Medicine or Advanced Therapy field, a regulatory consultant and a regulatory GMP inspector with international reach. Participants were invited to respond individually by means of a semi-structured interview process to six open questions: (i) Do you think this model could have a positive impact on the development of MTMM autologous therapies? (ii) Can you explain what major challenges/barriers such a model may face? (iii) Are there any regulatory requirements that are specific to either the European Union or the United States that could make the implementation of this model more challenging? (iv) How do you think this model may affect the whole development process for an MTMM autologous cell therapy product? (v) Do you think that this model could be modified to make it more feasible from a regulatory perspective, or is there an alternative model? (vi) What tractable science/technologies are available or required to enable this model?

For each of the manufacturing models and each of the questions posed, the panelists' responses were segmented into a series of discrete statements. Statements were then coded and assigned to emerging categories, which were then refined into a series of pivotal questions. Validation of the categorization process involved a review of the features of each category to ensure distinctiveness and to ensure that the ascribed questions reflected the statements that they subsumed. The outcome of this analysis was used to format and map the following discussion to each of the proposed models. Alternative manufacturing models emerging from the panelists' responses were also captured to solicit further assessment and comment.

Results

Manufacturing model 1: limited cell expansion

The model asserts that autologous cellular products manufactured by use of a minimal number of population doublings during culturing may reduce the extent of the characterization/validation studies needed to show comparability between manufacturing sites under a single product licence. The premise of the model is that limiting the number of *ex vivo* population doublings (eg, one or two) required to generate the therapeutic product (with or without an allowance for pooling) minimizes the risk factors associated with the manufacturing process and the product by (i) reducing the complexity of the manufacturing process, for example, fewer media changes/formulations, fewer raw materials, fewer manual manipulations and so forth and improving reproducibility, and (ii) reducing the risk of changes to the biological characteristics, physiological function(s) or structural properties of the cells associated with expansion of the cells before their return to the patient.

Can you ensure consistent cell function by defining a stable and predictable cell composition and the limits for acceptable changes?

The case for the limited expansion model was supported, with experts agreeing that minimizing the number of cell divisions required to generate efficacious autologous cell product for the majority of indications is inherently safer from the point of view of *in vitro* cell stability and potential for biodivergence.

However, from the regulator's perspective, cell manipulation may not necessarily lead to apparent changes in cell behaviour of the gross phenotype of the cells after *in vitro* culture. Even minimal expansion in culture is therefore judged to have the potential to alter cells in a way that is difficult to predict without subsequent testing of the biological

characteristics, function or structural properties of the cells (4,20–22).

The perspective shared by the experts was that a limited expansion model would be predicated on the cell seeding and expansion approach and on demonstrating that the risk of biological divergence or drift over time is more tied to the number of population doublings than it is to how the first doubling is carried out (accepting the maintenance of sterility and effective depletion of contaminating cells), that is, the more-than-minimal manipulation paradigm. Experts referred to the importance of establishing a scientific basis for the limits of safe expansion. This would enable controls to be set for the permissible number of passages and population doublings to minimize the potential for change [akin to the viral seed lot system used in vaccine production (23)] and for defining the edge of failure, that is, the point at which cells in culture begin to drift or acquire genetic and epigenetic changes. In emphasizing the need to establish these limits early in the development stage, current test systems were seen by some experts as lacking the sensitivity and specificity to adequately detect some of these cell transformations.

It will be important to understand the nature and extent of the changes to the manufacturing process and how they will affect the safety profile of the final product. In this context, some experts expressed the view that a stable cell line or a cell line that changes in a predictable manner should facilitate assessment of the impact of these changes, providing there is sufficient knowledge of the relevant quality attributes of the final product. Challenge studies that use non- or under-functioning lots (ie, purposely degraded or over-expanded) early in clinical development pathway are a key component (24). These would enable the criteria that provide limits for acceptable changes to be defined, for example, that distinguish cellular changes that are irrelevant to a product's clinical function from potentially unsafe alterations.

Can you ensure manufacturing and lot-to-lot consistency in light of donor-derived starting material variability?

The operational advantages of the less complex manufacturing processes associated with the limited expansion model were underlined, exemplified by a reduction in the prominent and cumulative risk factors associated with multiple, often manual, manipulation steps (eg, operator error/training, tracking/mix-ups, contamination and cross-contamination). However, despite the potential reduction in safety concerns and in operator induced variation, experts shared the view that variability associated with donor-derived starting material (ie, input variation) would still be the critical factor influencing the prospects for reproducible manufacturing.

The impact of both intra- and inter-individual variation on the quality of the starting material was stressed, in particular differences arising from the cell isolation procedure and associated sensitivities to operator technique, the tissue/organ biopsy site and the sample characteristics imposed by the disease state or other characteristics of the individual.

Experts referred to the need for a greater emphasis on identifying critical donor characteristics (eg, sex, age, weight, state of health, etc) and test criteria for donor material selection. This would permit minimum thresholds for justifying the process input to be established and patient specific end points relative to the characteristics of the of the patient to be derived. Linked to end-stage potency evaluation, an improved understanding of the pharmacokinetic/pharmacodynamic profile of the cell product was stressed as having a key role in relating cell function *in vitro* to preclinical benefit and appropriate dose and dose regimen design. Overall, a better understanding of the input variables that influence *ex vivo* expansion potential/efficiency and that affect process reproducibility and product outcomes in terms of the functional potential and kinetics of cells, it was suggested, would allow the quality control of the source and nature of starting materials. This would enable the determination of rational operating limits within which a predictable outcome can be assured in the process and for the product.

Can you define and characterize the safety factors/quality attributes of final product sufficient to ensure consistent cell function with limited material and time available for testing?

Cell product characterization—specifically identity, purity, potency and safety—underpins regulatory expectations for the assessment of process and product stability, reproducibility and comparability after a process change or across manufacturing sites. The regulatory expectations for the degree of assurance and stringency of the data required to demonstrate comparability will depend on the nature and extent of the change and the stage of product development. Some experts raised the question as to how the regulator decides what is sufficient, reflecting the current vigorous debate in this area (9–14).

The extent and depth of the testing program is determined by the potential impact of the changes on the physicochemical and biological properties of the product and in practice, the availability of suitable analytical techniques correlating critical quality attributes with the MOA or clinical efficacy and safety

of the product. The demonstration of comparability that bridges these changes could encompass extensive *in vitro* characterization, with or without nonclinical or clinical testing (or both) (25). From the regulator's perspective, with both US an EU regulatory bodies subscribing to ICH Q5E (25), the expectation is that comparability testing programs consider an assessment of the impact of changes to the product quality attribute profile caused by the manufacturing process change as it relates to the safety and efficacy of the product. A recent report by the Potency Working Group (formed by the ISCT Process and Product Development Committee) has asserted that without the inclusion of measures of biological activity in the testing program (including surrogate measures of potency that allow prediction of activity *in vivo*), product comparability cannot be established after changes, even minor changes, are made to the manufacturing process without nonclinical or clinical testing (or both) (15). This would represent the worst-case scenario from a developer's perspective, a viewpoint that was shared by some of the experts.

The challenge, given the large variety of potential autologous cell therapies under development, will therefore be to identify potential biomarkers and develop potency assays that have relevance to the intended clinical use. If such measures could be developed early enough in the product lifecycle, that is, as the manufacturing platform matures from Phase I to commercial lockdown, the view was that these tests could provide more discriminating data than *in vivo* preclinical trials in contrived animal models. By allowing prediction of activity *in vivo* beyond the measures required for lot release, characterization profiles could be used to differentiate critical and non-critical characteristics, to demonstrate that routine potency is achieved and ultimately, to reinforce the demonstration of comparability.

Even if the MOA(s) of the cell product can be elucidated, experts agreed that developing valid and quantitative predictive surrogate tools applicable to such extensive testing in the autologous setting, particularly in the limited expansion setting, would be challenging. This would require significant advances in the development of new rapid, nondestructive, inexpensive, highly precise and sensitive characterization technologies and test methods to overcome constraints related to small lot sizes, short shelf lives and the clinically limited time available for pre-clinical and lot release testing. Examining other possibilities, experts questioned whether the pooling of donor samples from an individual patient could provide a solution to product lot volume limitations. Concerns were raised relating to inter-site variability (intra-patient) and ethical compliance surrounding the use of multiple biopsy procedures for the supply of validation material.

Complications arising from the lack of harmonization and standardization of assays and the requirement for more predictive safety and functional biomarkers for use in biologically relevant animal models and for qualifying additional surrogate end points was emphasized. This reflects the emphasis currently placed on standardization of potency assays and cell characterization by organizations such as the ISCT and the Alliance for Regenerative Medicine in the United States and the British Standards Institution in the United Kingdom. According to one panelist, this also underlines the need for more sophisticated genetic, epigenetic and proteomic analyses that might be predictive of increased risk or (pre)clinical benefit and that might detect changes earlier than the corresponding clinical end point.

Manufacturing model 2: incremental validation (a risk-based approach)

The premise of the model is that MTMM autologous cell therapies are manufactured at multiple sites, released "proportional to the degree of risk" on the basis of the product release specifications found in the original license and incrementally validated after marketing (continuous validation). The model asserts that a stratified risk-benefit—based approach supported by post-market surveillance would allow incremental cost-effective scale out/roll out to additional manufacturing sites, reducing the extent of the characterization/validation studies needed to show comparability between manufacturing sites under a single product licence.

Can you ensure GMP uniformity across multiple manufacturing sites?

The challenge of manufacturing consistency and conformance to GMPs for small developing companies and product developers in academic or hospital settings, which in many cases are transitioning from non-GMP facilities or facilities accredited as tissue establishments, is well recognized (26). Experts agreed that replicating and qualifying additional facilities to GMP standards is expected to be relatively straightforward, notwithstanding the business risks associated with the increase in capital (and operational) expenditure and the time and cost involved in regulatory compliance. Implementing GMP facilities in parallel (ie, the N model)[1] from the outset, that is, under a single market authorization application variation, could significantly reduce the time and cost for data submission, particularly if the

inspection of the facilities could be streamlined by utilizing the same team of regulatory inspectors. However, despite these advantages, one expert was emphatic that this approach would not be commercially acceptable.

Often requiring new capabilities within an organization and its people, opportunities to minimize differences between sites in key areas of risk and ensure consistency and quality were highlighted. For example, standardizing equipment, utilities, materials and supplies, implementing multi-site control and management strategies to mitigate risks of adding people to the process, provision of a centralized (re)training at a reference site and implementing a single overarching quality system and control plan for manufacturing process oversight.

Experts also specified the importance of understanding the regulatory environment in different geographies. This is essential to reduce uncertainty in the data requirements for GMP compliance (eg, manufacturers in the United States are exempt from many of the GMP requirements during Phase I trials) and to reduce the impact of differing healthcare management, administration and legal control systems on GMP facilities and on clinical trial design and authorization.

Can you ensure a consistent MTMM autologous product by defining reliable product release specifications?

A well-defined manufacturing process with its associated process controls ensures that acceptable product is produced on a consistent basis. However, with limited manufacturing experience and under traditional process validation approaches (with the use of a limited number of product consistency lots) and end product quality control systems, manufacturing processes are often poorly specified and locked in to narrow specification criteria at the time of approval. In this context, experts referred to the impact of input variability associated with donor-derived starting material and the ethical concerns surrounding the acquisition of the multiple product cell lots that are required for such traditional process validation studies (eg, are repeated procedures for draining patient bone marrow for use in validation studies ethically justifiable?).

From a regulatory perspective, it was perceived that the tests and analytical procedures chosen to define the product specifications under a traditional end-product testing–based product release regime generally would not be considered adequate to assess the impact of manufacturing process changes or site transfer. Typically, these specifications are chosen to confirm the routine quality of the product (eg, sterility, identity) rather than to fully characterize it. A manufacturing process change is likely to require a complete or limited repetition of the characterization activity that was conducted for the market authorization application (25). Despite the expectation that the level of characterization required by the regulator may be reduced with the addition of subsequent manufacturing sites beyond a certain threshold (eg, $n > 6$), experts agreed that this level of testing would still present significant practical challenges in the autologous setting for the reasons already described.

The perspective of two panelists was that completion of process validation studies should be sufficient for regulatory approval of additional manufacturing sites, referring to analogous approaches for bone marrow transplantation and the preparation and production of radiopharmaceuticals in positron emission tomography centers. The challenge for autologous cell therapy manufacturers, however, is in how to apply process validation to a manufactured lot of patient cells when that same lot is intended for treatment of the patient.

New concepts within the process validation guidance (27,28), which put forward continuous process verification as a more progressive and graded approach, afford manufacturers with new possibilities. From a European perspective, panelists suggested that complete validation of the registered process and control strategy in the first site might permit a reduction in the characterization burden for the validation of processes at subsequent GMP-compliant manufacturing sites. The expectation, however, was that critical phases of manufacture and material control not addressed by application of the finished product specification alone would still require additional testing.

Typically, the process validation study must be completed successfully and a high degree of assurance in the process must be achieved before commercial distribution of a product. From a US perspective, one panelist advocated a strategy analogous to the bone marrow transplantation approach, which was developed with site accreditation, adherence to standard operating procedures and classification or validation of sites through the practice of the therapeutic approach. Under US Food and Drug Administration (FDA) process validation guidance (27), the process performance qualification protocol can be designed to release process performance qualification lots for patient treatment before complete execution of the protocol steps and activities, that is, concurrent release. The approval of subsequent manufacturing sites could be based on a concurrent release program in which samples from each lot or a significant proportion of lots can be evaluated in a more extensive biosafety testing program in non-clinical models. This would provide statistical

confidence that clinical product manufactured by means of the qualified process routinely exhibit consistent potency while data are accrued in clinical practice under a continued process verification phase.

These approaches call for an evaluation of safety specifications that take into account the benefits of the cell therapy, corresponding levels of perceived risks, the possible practical limitations and the possibilities for risk mitigation and management. Expectations were that these risk-based product release approaches would be discouraged by many regulatory bodies because of the potentially wide variety of cell types and treatments, their inherent biological variability and complications caused by the underlying natural disease course or other co-morbidities associated with many autologous products.

However, with the European Medicines Agency and FDA placing more emphasis on post-market surveillance, some experts indicated that such approaches may be appropriate for a number of specific fast-track or orphan designation regulatory pathways to expand access to treatments for unmet medical conditions and ultra-rare or life-threatening diseases. These include the fast-track, priority review and accelerated approval programs in the United States, which have recently been expanded under the FDA Safety and Innovation Act 2012 (FDASIA) to allow sponsors to request that their therapy be designated as a "breakthrough therapy" (29).

One panelist pointed to regulatory trends in Japan and South Korea that consider different evaluation approaches on the basis of adaptive licensing or conditional marketing approvals. These approaches are grounded on stepwise learning and iterative phases of data accrual and regulatory re-evaluation, which allows commercial sale in certain instances while pivotal trials are underway.

In South Korea, for example, this has recently led to the approval of an autologous bone marrow–derived mesenchymal stromal cell (MSC) therapy product (HeartiCellgram-AMI; PharmiCell Co Ltd) and the world's first allogeneic, off-the-shelf MSC-based product (Cartistem; Medipost Co Ltd). According to Ancans (30), a similar regulatory decision has seemingly been adopted for the Osiris Therapeutics Inc allogeneic MSC product Prochymal. In May 2012, the company was granted an authorization for the treatment of acute graft-versus-host disease in children under Health Canada's Notice of Compliance with conditions, which is an authorization to market on the condition that the manufacturer undertakes additional studies to verify the clinical benefit (30). It should be noted that Prochymal has since received approval by the New Zealand Regulatory Agency (Medsafe) under their priority review scheme; it is currently available in the United States under an "Expanded Access Program" (so-called "compassionate use"), has received an Orphan Drug designation in the European Union and will be evaluated in Switzerland under their agency's (Swissmedic) "Rapid Authorization Procedure." In Japan, too, there is emerging evidence that induced pluripotent stem cell therapies may be given an easier path to the clinic in the near future as the government drives to capitalize on the technology. A prospective revision in the drug law is expected to fast-track therapies that appear to be effective in Phase II or Phase III trials (31).

Can you ensure MTMM autologous product consistency by defining a set of critical process parameters and material attributes?

That the "product is the process" currently means that there are very significant couplings between the design of the product and the design of the process and production system. A critical variable still to be established for cell therapy products is the allowable variation in the critical parameters required for product performance, for example, the key components of the product specification defining what must be achieved by manufacturing (18). However, the interpretation and comparison of data used to support GMP sterile manufacture compliance (eg, clean room classification, sterility testing), materials specification, clinical qualification and product release (eg, phenotypic markers and potency assays) is hampered by a lack of standardization in applicable test methods and acceptance criteria. Experts referred to the importance of developing uniform International Standards and additional consensus guidelines for the development, validation and standardization of capable quality control (QC) assays and measurement systems traceable to reference standards.

In terms of identifying differences between sites and key areas of risk, the development of a stable, well-characterized reference or surrogate cell line(s) was emphasized by some experts as a key enabler for process validation and identifying opportunities for risk mitigation and management. This aligns with the recent proposal by Viswanathan *et al.* (32) on the use of these cell-based reference materials to establish comparability among mesenchymal stromal cell preparations, which describes the benefits and requirements for establishing cell-based reference materials and their global distribution. Combined with corresponding precise and validated tests, this would allow tolerance for critical-to-quality attributes across multiple sites (i.e; the allowable variation) to be

derived and processes to be developed where the achievable variation can be reliably demonstrated to be better than the allowable variation. This would assist the QC and normalization of quantitative assay data, the move from customized processes to the development of standardized protocols, the qualification of processing equipment and implementation of alternative continuous process validation approaches.

The sensitivity of therapeutic cells to process conditions and the difficulty of autologous product characterization enforce greater reliance on process understanding and control to ensure product safety and efficacy. Echoed by the US regulator (27,33) but not explicitly accepted by the EU regulator despite indications to the contrary (28), some experts referred to the advantages of quality design–led and continuous process verification approaches enabled by the principles of quality by design (QbD). The QbD approach focuses on building quality into the product through a better assessment and mechanistic understanding of the effect of critical process parameters on product critical-to-quality attributes, linking the safety and efficacy of a product, in part, to product components and manufacturing process parameters. The view expressed by some experts was that the application of QbD would allow for adjustments of operating parameters or material attributes within potentially a larger design space, without the need to readjust specification acceptance criteria or to seek regulatory approval for post-approval changes. This would allow easier introduction of innovative new technologies into an existing manufacturing pipeline for example, which is currently hampered by the rigidity of manufacturing processes that are often fixed within poorly specified and narrow process validation parameters under traditional process validation approaches.

Experts specified the need for improved scale-down model systems and advances in on-line, real-time process and end-point monitoring and sensor technology. Such technology advances would remove many of the obstacles to the implementation of QbD approaches, and provide a step change in process control capability and the potential for real-time product release testing. By way of enabling continuous process verification, improvements in the detection, understanding and control of variability and hence the consequences of changes in process or product quality are expected to substantially reduce the extent of the characterization studies needed to show comparability between manufacturing sites under a single product licence.

Manufacturing model 3: closed or functionally closed automated manufacture

The model asserts that MTMM autologous cellular products manufactured by means of a closed and automated process may reduce the extent and depth of the characterization and/or validation studies needed to show comparability between manufacturing sites under a single product licence. The premise of the model is that a closed or functionally closed automated device-based machine is used to manipulate (cell expansion) and process the cells. This so-called "GMP in-a-box" device can be validated to design specifications by means of a cell/product-specific protocol within a fully closed processing environment. A single Advanced Therapy Medicinal Product (ATMP) licence/Biologics Licence Approval (BLA) would still be required, but only the machine would need to be validated for a chosen indication/protocol and not the sites in which it would be used.

How do you licence a device that produces a medicinal product?

There was consensus that engineering and production system design solutions to the development of highly standardized, closed or functionally closed automated production systems may go some way to achieving replication of the unit process of production and achieving comparability. The view was that such "GMP in-a-box" systems would enable simpler scale out/roll out of MTMM autologous therapies to multiple distributed sites by reducing the impact of the environment in which the closed processes are situated on the process stream. Advances in such process technologies could provide opportunities to exploit the potential for locating closed processes and their supporting systems within non-classified room environments, or so-called Controlled Not Classified manufacturing settings. This could potentially lower infrastructure and operational costs and the time and cost involved in regulatory compliance for both existing and new facilities.

From a regulatory perspective, panelists considered that a closed or functionally closed automated production system, by removing operator variation and the external environment, that is, the extrinsic contamination risk from the manufacturing process, will bring the process under control and make process variation more predictable. Process development and validation would be intrinsically more straightforward, provided it was founded on Factory Acceptance Testing of the built system and its qualification at each site (including the software).

However, experts emphasized that the machine and the location or space in which it is housed must be controlled and maintained under a Quality Management System for every manufacturing and QC step as scale out occurs, whether it be through installation of additional automated systems in the original facility, in distributed manufacturing sites in

hospital settings or at the bedside. This would necessarily involve evolving GMPs that are better suited to the setting in which the closed or functionally closed manufacturing takes place, for example, GMPs for nurses or health professionals. Under these practices, appropriate risk-based approaches for controlling the risk of contamination and ensuring safe operations can be used to define the level of process and facility hygiene control and to mitigate risks of human error or interference with system hardware and controlling software.

Despite the hesitancy of the bioprocessing industry to enter the scaled cell manufacturing space (34), one panelist pointed out that the development of manufacturing technologies suitable for producing limited clinical product designated for an individual was evolving, for example, with devices such as the Quantum Hollow Fibre Bioreactor (Terumo BCT) and the Xpansion Bioreactor (ATMI). Most experts agreed that if the advantages of closed or functionally closed expansion systems are to be realized, advances in the development and integration of GMP-compliant automated solutions amenable to certain open upstream operations (eg, cell isolation/cell purification processes) were needed. In terms of downstream processes, if the autologous cell therapy product is to be supplied through distributed manufacturing sites rather than at the bedside, the requirement for improved preservation and transport enabling technologies to eliminate GMP-regulated process steps for preservative removal or thawing steps at the point of use was considered critical.

Experts referred to the regulatory challenges involved in locating the system at the bedside, centered on whether the system should be validated as a piece of equipment or as a device for producing a product licensed under ATMP or Human Cells, Tissues and Cellular and Tissue-based Product (HCT/P) regulations. One panelist cited the claims and intended uses of the CliniMACs Prodigy (Miltenyi Biotec) and Cellution (Cytori Therapeutics Inc) systems as examples of where the regulatory lines can become blurred, particularly with the current lack of clarity and harmonization in the interpretation of non-homologous use.

With such point-of-care manufacturing not envisaged under existing US and EU regulatory frameworks and particularly with little regulatory heritage in this area, the challenges from a regulatory perspective are multifactorial. For example, determining where GMP starts for a bedside device producing an ATMP or HCT/P, how these closed or functionally closed systems fit the environment in which they are housed and how both can be inspected, how lot release criteria for potency and the fidelity of the products they produce is determined and the practicality of procedures by which a qualified person can release final product that is produced for immediate administration into the patient. Experts also expressed concerns related to how avoidance of compliance with quality standards can be prevented, for example, "off label" use of products or inappropriate re-classification of the treatment beyond the mandate of competent authorities. This was highlighted as a particular concern under regulatory landscapes in which the definition of cell-based products and the latitude for autologous use is less well defined than it is in Europe (14,35,36). Clarification of the US and EU regulatory pathways for the licensing of devices that produce an ATMP or HCT/P and on the classification of products applied to the intended non-homologous or homologous use of the cells at the point-of-care was recognized as critical to the progression of product development and regulatory compliance strategies in this area.

Alternative manufacturing models

In assessing each of the proposed manufacturing models, the following alternative models for addressing the challenges for the scale out/roll out of MTMM autologous cell therapy products emerged from the panelists' responses.

Distributed manufacturing model: moving toward clinical Centers of Excellence

Grounded on shifting the development, manufacture and supply of autologous cell therapies away from the donor product, biologics/drug paradigm toward the transplant product paradigm, the premise of this model is to move the MTMM autologous product development and therapeutic trial process into the hands of the medical practitioner. Regulated under an evolutionary variant of Hospital Exemption in Europe (17) inside dedicated clinical Centers of Excellence for particular therapeutic areas, this model shifts away from the "cell as a product" concept toward an integrated service/tool—based model of product development and manufacture. In this model, sponsors under GMP provide the materials/components/intermediates for cell expansion and testing, the cell expansion platforms and associated standardized protocols to clinical Centers of Excellence, where the cell expansion process and therapeutic approach is optimized under the control of the medical practitioner.

In striving to balance patient risk (and potential benefit), promote innovation and early access to promising therapies, this model asserts that by creating dedicated Centers of Excellence and permitting the roll out of the standardized process

Table I. Perspectives of thought leaders on the relative strengths and weaknesses of each manufacturing model.

Strengths	Weaknesses
Model 1	
Inherently safer product with respect to *in vitro* cell stability and potential for bio-divergence. Reduces cumulative risk factors in the product	Even minimal expansion is judged by regulators to alter cells in a way difficult to predict without biological testing
Minimizes potential for change if controls for the permissible number of passages and population doublings can be established	Defining the limits of safe expansion may be restricted by lack of sensitivity and specificity of current test systems for detecting cell transformations
Reduces cumulative risk factors in the manufacturing process by reducing complexity and variation in the process	Donor-derived input variation will influence *ex vivo* expansion potential/efficiency and the prospects for reproducible manufacturing
Reduces the risks associated with pooling of samples from the same patient, providing an opportunity to overcome product lot volume limitations for validation and release testing in the autologous setting	Expected that pooling would be highly scrutinized by regulators because of concerns related to donor inter-site variability and ethical compliance surrounding use of multiple biopsy procedures
Limited cell processing technology barriers	May have limited application for more complex products or disease states in which high doses are required or there is an insufficient potent cell reservoir
EU and US regulatory approaches likely to be similar	
Model 2	
Overcomes current rigidity of poorly specified manufacturing processes that are based on limited validation parameters. Potentially easier introduction of innovative new technologies into an existing manufacturing pipeline	Model is underpinned by replication of GMP systems across multiple sites, but comparison of data to support compliance is hampered by a lack of international standardization
Aligns with QbD-led approaches and new concepts within the process validation guidance	Acceptance of QbD approaches differs between EU and US regulators
Design of process validation protocols allows concurrent release of validation lots for patient treatment at each site on the basis of lot release test criteria and concurrent biosafety testing in non-clinical models	Expected that regulators would view product release regimes on the basis of end-product specification test criteria as inadequate for assessing impact of manufacturing changes
The integrated system of parametric release could be used to eliminate certain specific tests of the finished product	May require availability of sufficiently rapid and precise surrogate measures of potency that overcome the time and volume constraints
Continuous validation might permit a reduction in the characterization burden for the validation of processes at subsequent GMP-compliant manufacturing sites	Without advances in process control capability, it is expected that critical phases of manufacture and material control would still require additional testing
May be appropriate for a number of specific fast-track or orphan designation regulatory pathways under current regulatory frame works	Sufficient material volumes for validation testing and administration to the patient may be limited
Model 3	
Permits straightforward replication of the unit process of production	Requires Factory Acceptance Testing of the built system
Removes operator-derived variation and the external environment from the manufacturing process, making the process more controllable, less susceptible to extrinsic contamination, variation more predictable and validation intrinsically simpler	Built system requires installation, operational and performance qualification at each site. May also require computer systems/ software compliance
Provides potential for locating manufacturing systems within non-classified room environments or Controlled Not Classified settings	Critical manufacturing process steps must be amenable to automation
Lowers facility/site infrastructure costs and operational costs and reduces time and cost involved in regulatory compliance	Poor capability and lack of integration of largely manual upstream processes, for example, cell isolation/purification procedures
Reduces risk of contamination and cross-contamination. Potential for reducing the autologous donor testing requirements in the EU	Does not eliminate need for GMP processing steps for preservative removal and thawing if product is to be supplied through distributed manufacturing
Under a Quality Management System and internal QC, only the built system may need to be validated for a chosen indication/ protocol instead of the sites in which it is used	Regulatory uncertainty on whether systems for point-of-care manufacturing should be validated as a piece of equipment or as a device for producing a medicinal product
As a way of addressing continuous validation approaches, may permit components of the performance qualification to be carried out at multiple sites with cell line surrogates rather than product	Regulatory uncertainty related to oversight of the manufacturing process and the clinical supply of product in point-of-care settings
Automated closed or functionally closed cell processing technologies are rapidly evolving	

Table II. Perspectives of thought leaders on multi-site enabler hotspots for the reproducible manufacture of MTMM autologous cellular products.

Hotspot	Thought leader perspectives
Input variation	Reducing the impact of donor-derived starting material variability on the manufacturing system: ○ Understanding and quantifying critical donor characteristics (sex, age, weight, disease state, etc) for ■ Input stratification ■ Patient-specific end points ■ Pharmacokinetic/pharmacodynamic models and dose regimen design ○ Develop process designs that tolerate donor-derived variability in the inputs
Upstream/downstream processes	Reducing process and product variation: ○ Advance transformative improvements in preservation and transport enabling technologies to eliminate GMP-regulated process steps for preservative removal or thawing ○ Develop automated functionally closed systems for cell isolation/purification
Specification setting	Defining minimal manipulation: ○ Establish the limits of safe expansion and define the edge of failure ○ Set controls for permissible number of passages and population doublings; establish limits of acceptable change ○ Enable challenge studies using non- or under-functioning lots (ie, purposely degraded or over-expanded) early in clinical development ○ Improve sensitivity and specificity of cell transformation test systems
In vitro characterization	Overcoming the time and volume constraints for pre-clinical and lot release testing in the autologous setting: ○ Develop new rapid, non-destructive, inexpensive, highly precise and sensitive characterization technologies and test methods
"GMP in-a-box"	Developing automated closed or functionally closed, regulatory-compliant manufacturing systems for cell expansion: "GMP in-a-box": ○ User requirement specification applied to ATMP or HCT/P production in distributed sites, hospital settings and at the point-of-care ○ Explore opportunities for locating manufacturing systems within Controlled Not Classified settings ○ Determine GMPs that are better suited to the bedside setting ○ Determine the regulations for licensing a device that produces a medicinal product and how they can be enacted in hospital settings ○ Explore hybrid process registration strategies applicable to "GMP in-a-box" systems: ■ Validate the registered process and control strategy through use of a standard set of cell lines (+VE and −VE controls for function) ■ Verify the product batch by reduced point-of-release testing on the basis of detecting out-of-specification behavior
Standardization	Establishing methods of comparability: ○ Develop stable, well-characterized surrogate cell line(s) as a reference or "ruler" with the necessary specification and precision ("units on the ruler") ○ Link their use to automated processing systems as a way of addressing continuous validation approaches ○ Develop automated methods for their manufacture/banking and enabling systems for global distribution
Process validation	Designing process validation studies sufficient for regulatory approval of additional manufacturing sites: ○ Link the use of surrogate cell lines to "GMP in-a-box" systems as a way of addressing continuous validation approaches ○ Develop process control capabilities to permit continuous process verification approaches and expand the use of concurrent product release approaches
Regulatory framework	Clarifying regulatory pathways: ○ Develop better tools to support an objective assessment framework that: ■ Balances patient benefit with levels of risk ■ Balances regulation at translational bottlenecks (eg, comparability) ■ Promotes innovation ■ Accelerates clinical experience and early access to promising autologous therapies ○ Debate the role of regulator and other stakeholders in the risk/benefit decisions, specifically "GMP in-a-box" and point-of-care manufacturing ○ Capture learning from real product experiences to develop better tools for a risk/benefit framework ○ Explore opportunities for investigator-led initiatives for patient-designated clinical production within clinical Centers of Excellence under the scope of the practice of medicine

to distributed manufacturing sites, an effective therapeutic network can be built to coordinate best practices and accelerate clinical experience in the cell therapy space. In principle, through an open development mechanism intended to make clinical trial design and data transparent, the model would stimulate both intellectual and financial investment in later-stage cell therapies This would open opportunities for co-development of therapies/test regimes with industry and for facilitating the pull and adoption of new treatments as the standard of care in clinical practice.

The model raises the following questions: Can you ensure a chain of command and associated reporting requirements for data collection, for example, who verifies QC/QA and lot release of the final product? Who determines what is safe and what is not, in terms of dose and delivery of the cell therapy? Can you ensure control of the product production process and prevent "off-label" use? Who funds the development and operational costs of the process and how are the operator and the therapeutic sponsor reimbursed? Can the model be expanded and applied to banking material for acute indications?

Hybrid manufacturing model: maturing the concepts of models 1–3 for distributed manufacturing

The premise of this hybrid model is a move toward a more controlled manufacturing process, building and integrating the concepts of model 1 and model 2. The hybrid model would realize the lower risks associated with limited expansion and overcome time- and volume-limiting constraints while maintaining sterility and managing risk through the development of a closed or functionally closed automated device ("GMP in-a-box") that manufactures an MTMM autologous therapy at the factory or at the point-of-care. This model asserts that by minimizing the impact of manufacturing site and operator variability and maximizing the reduction of risk, the extent of the characterization/validation studies needed to show comparability between manufacturing sites under a single product licence may be reduced.

Summary

This paper addresses one of the key current challenges in cell therapy manufacturing. It has used the literature and views of a panel of key thought leaders in the industrial and regulatory community to define critical areas that must be addressed to allow clinically led MTMM autologous therapies to be rolled out in the event of their success at a single site. We have proposed three prospective manufacturing models, considered how they might be enabled and tested their prospects for addressing the challenge of product comparability under the principles of the existing regulatory landscape. Alternative manufacturing models emerging from the panelists' responses were also captured to solicit further assessment and comment.

The existing regulations remain uncompromising with respect to the level of assurance required to demonstrate comparability after the roll out of processes to multiple manufacturing sites post-clinical trial, either within the same (N+1 model) or different jurisdictions (N+M model). It is not yet clear which of these manufacturing and distribution approaches will be most suitable under the existing regulatory frameworks. Each manufacturing model has its strengths and weaknesses, reflecting the varying perspectives of panel (Table I).

Although many of the manufacturing and operational constraints identified in this paper are well understood and common to all cell therapy manufacture, the perspectives and insights of the panel have identified specific and additional challenges for the manufacture of MTMM autologous cell therapies. Driven by the need to scale out manufacture while containing cost of goods and costs of validation and by the potential need to manufacture therapies at the point-of-care or in hospital settings, Table II summarizes the perspectives of the thought leaders on where operational, technological and scientific improvements should be prioritized and where new enabling science is still required. Extending across all of the manufacturing models, the following discussion expands on the requirements and opportunities identified in Table II.

With each product lot representing a unique donor, differences between tissue sources and individual donor characteristics, compounded by the poor capability of upstream isolation methods, create greater potential for product variability in the autologous setting. Better quality control of the source and nature of the donor-derived starting material is needed so that minimum thresholds for justifying the process input can be established and patient-specific end points relative to the characteristics of the patient can be derived.

To maximize the favorable safety and risk profile provided by short-term autologous cell culture, a scientific basis for the limits of safe expansion must be established. This would allow controls to be set for the permissible number of passages and population doublings to minimize the potential for change.

Scale out efficiencies for individualized production would be facilitated by the transition to automated closed or functionally closed and regulatory-compliant manufacturing technologies ("GMP in-a-box" systems), suitable for producing limited clinical ATMPs or HCT/Ps designated for an individual.

With the wide variety of potential tissue sources, advances in the development of integrated, GMP-compliant, closed automated platforms amenable to upstream cell isolation/purification procedures are required to reduce intra-donor and inter-donor–derived variability in expansion process efficiency. They may also provide the potential for within-patient cell pooling, if ethically justifiable.

Improvements in preservation and transport enabling technologies to eliminate GMP-regulated process steps for preservative removal or thawing will be transformative for the development and supply of autologous cell therapy products through distributed manufacturing sites.

Clarification of the US and EU regulatory pathways, both for the licensing of devices that produce an ATMP or HCT/P and for the classification of products applied to the intended non-homologous or homologous use of the cells at the point-of-care, is required if alternative business models are to be progressed in this area.

Despite the emerging safety profile of autologous therapies, arguably clinical applications for MTMM autologous therapies will continue to be in patients with unmet medical conditions and ultra-rare or life-threatening diseases under "special" regulatory pathways. If regulatory bodies are to enhance proactivity in their stated aim to protect, promote and improve public health, better tools are required to support an objective assessment framework that balances patient benefit with corresponding levels of risk, promotes innovation, expedites the demonstration of comparability and accelerates clinical experience and early access to promising autologous therapies.

Further debate on the role of regulators and stakeholders in the risk/benefit decisions and on the process for formation of the regulation is called for, specifically for concepts such as "GMP in-a-box" and point-of-care manufacturing. Developers will need to openly engage with the regulator to inform this framework by capturing the learning from real product experiences.

The emergence of new regulatory paradigms such as those recently adopted in South Korea, Japan and Australia, for example, could affect national competitive advantage. The intense debate between regulators, law makers and practitioners (37–41) underscores the need for clarification within existing US and EU regulatory frameworks on the role and opportunities for investigator-based initiatives for patient-designated clinical production within clinical Centers of Excellence under the scope of the practice of medicine.

As proposed by Rao (personal communication, 2013), the development of stable, well-characterized surrogate cell line(s) is fundamental to establishing methods of comparability. Linking their use to automated processing systems as way of addressing continuous validation approaches, these surrogates, acting as a reference or "ruler" with the necessary specification and precision ("units on the ruler"), could provide an inexpensive and simple way to compare manufacturing processes at multiple sites or between processing equipment.

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References

1. Foley L, Whitaker M. Concise review: Cell therapies: the route to widespread adoption. Stem Cells Translat Med. 2012;1:438–47.
2. Mason C, Hoare M. Regenerative medicine bioprocessing: building a conceptual framework based on early studies. Tissue Eng. 2007;13:301–11.
3. Ahrlund-Richter L, De Luca M, Marshak DR, Munsie M, Viega A, Rao M. Isolation and production of cells suitable for human therapy: challenges ahead. Cell Stem Cell. 2009;4:20–6.
4. Committee for Advanced Therapies (CAT) and CAT Scientific Secretariat. Challenges with ATMPs and how to meet them. Nature Rev Drug Discover. 2010;9:195–201.
5. Salmikangas P, Celis P. Current challenges in the development of novel cell-based medicinal products. Regul Rapporteur. 2011;8:4–7.
6. Van Wilder P. Advanced therapy medicinal products and exemptions to the Regulation 1394/2007: how confident can we be? An exploratory analysis. Frontiers Pharmacol. 2012;3:1–9.
7. VALUE Project Final Report: Regenerative medicine value systems: navigating the uncertainties. 2012:1–73. Available at: http://www.biolatris.com/Biolatris/News_&_events_files/VALUE%20Final%20Report.pdf. Accessed March 2013.
8. McCall M, Williams DJ. Cell Therapy distributed manufacturing: managing costs and risks. Cytotherapy Suppl. 2013;15:S51.
9. Freeman M, Fuerst M. Does the FDA have regulatory authority over adult autologous stem cell therapies? 21 CFR 1271 and the emperor's new clothes. J Translat Med. 2012;10:1–5.
10. Lttleman AS. Enforcement discretion: How can FDA more reasonably regulate autologous stem cell procedures? FDLI's Food and Drug Policy Forum. 2012;2:1–14.
11. McAllister TN, Audley D, L'Heureux N. Autologous cell therapies: challenges in US FDA regulation. Regen Med. 2012;7:94–7.

12. Werner M, Mayleben T, Van Bokkelen G. Autologous cell therapies: the importance of regulatory oversight. Regen Med. 2012;7:100–3.
13. DeFrancesco L. Adult stem cell therapies walk the line. Nature Biotechnol. 2012;30:739–41.
14. Bianco P, Barker R, Brustle O, Cattaneo E, Clevers H, Daley GQ, et al. Regulation of stem cell therapies under attack in Europe: for whom the bell tolls. EMBO J. 2013;32(11):1489–95.
15. Bravery CA, Carmen J, Fong T, Oprea W, Hoogendoorn KH, Woda J, et al. White Paper: Potency assay development for cellular therapy products: an ISCT review of the requirements and experiences in the industry. Cytotherapy. 2013;15:9–19.
16. US FDA. Title 21 CFR Part 1271 Human Cells, Tissues and Cell and Tissue Based Products. 2001. Available at: http://www.gpo.gov/fdsys/pkg/CFR-2011-title21-vol8/pdf/CFR-2011-title21-vol8-part1271.pdf. Accessed March 2013.
17. European Commission. Regulation 1394/2007 for Advanced Therapy Medicinal Products. 2007. Available at: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2007_1394/reg_2007_1394_en.pdf. Accessed March 2013.
18. Williams DJ, Thomas RJ, Hourd PC, Chandra A, Ratcliffe E, Liu Y, Archer JR. Precision manufacturing for clinical-quality regenerative medicines. Phil Transact R Soc A. 2012;370:3924–49.
19. Karkaria U. Dendreon to cut 117 Atlanta jobs. Atlanta Business Chronicle. 2011. Available at: http://www.bizjournals.com/atlanta/news/2011/09/14/dendreon-to-cut-117-atlanta-jobs.html?page=all. Accessed February 2013.
20. European Medicines Agency (EMA)/Committee for Advanced Therapies (CAT). Reflection paper on the classification of ATMPs. EMA/CAT/600280/2010. 2012:1–8. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/12/WC500136422.pdf. Accessed April 2013.
21. Carpenter MA, Couture LA. Regulatory considerations for the development of autologous induced pluripotent stem cell therapies. Regen Med. 2010;5:569–79.
22. Baum E, Littman N, Ruffin M, Ward S, Aschheim K. White paper: Key tools and technology hurdles in advancing stem-cell therapies. 2013:1–21. Available at: http://alliancerm.org/page/science-and-technology. Accessed November 2013.
23. Kesler DA, Siegal JP, Noguchi PD, Zoon KC, Feiden KL, Woodcock J. Regulation of somatic-cell therapy and gene therapy by the Food and Drug Administration. N Engl J Med. 1993;329:1160–73.
24. Pritchett T, Little L. "Hard Cell". Bioprocess Int. 2012;10:36–48.
25. European Medicines Agency (EMA). ICH Topic Q5E. Note for guidance on biotechnological/biological products subject to changes in their manufacturing process. 2005. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002805.pdf. Accessed April 2013.
26. Pearce KF, Hildebrandt M, Greinix H, Scheding S, Koehl U, Worel N, et al. Regulation of advanced therapy medicinal products in Europe and the role of academia. Cytotherapy. 2014;16:289–97.
27. US FDA. Guidance for Industry. Process Validation: General Principles and Practices. 2011. Available at: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM070336.pdf. Accessed April 2013.
28. European Medicines Agency (EMA): Guideline on Process Validation: Draft (EMA/CHMP/CVMP/QWP/70278/2012-Rev1). 2012:2–11. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/04/WC500125399.pdf. Accessed April 2013.
29. FDA/CDER. Breakthrough Therapies. FDA/CDER Small Business Chronicles. 2013; January 15: 1–2. Available at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/UCM335628.pdf. Accessed January 2013.
30. Ancans J. Cell therapy medicinal product regulatory framework in Europe and its application for MSC-based therapy development. Frontiers Immunol. 2012;3:1–8.
31. Cyranoski D. Stem cells cruise to clinic: Japanese study of induced pluripotent stem cells aims to demonstrate safety in humans. Nature. 2013;494:413.
32. Viswanathan S, Keating A, Deans R, Hematti P, Prockop D, Stroncek DF, et al. Soliciting strategies for developing cell-based reference materials to advance mesenchymal stem cell research and clinical translation. Stem Cells Dev. 2014. EPub ahead of print. Available at: http://online.liebertpub.com/doi/pdf/10.1089/scd.2013.0591. Accessed March 2014.
33. US FDA. ICH Q8 (R2): Pharmaceutical Development. US Fed. Reg. 2009; 71(98). Available at: http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073507.pdf. Accessed March 2013.
34. Deans R. Regulation, manufacturing and building industry consensus. Regen Med. 2012;7(6 Suppl):78–81.
35. Sipp D, Turner L. US regulation of stem cells as medical products. Science. 2012;338:1296–7.
36. Wall D. Update from the ISCT Australia/New Zealand Executive Committee: New access to novel and unproven therapies. ISCT Telegraft. 2012;19:1–2.
37. Maciulaitis R, D'Apote LD, Buchanan A, Pioppo L, Schneider CK. Clinical development of advanced therapy medical products in Europe: evidence that regulators must be proactive. Mol Ther. 2012;20(3):479–82.
38. Ehmann F, Amati MP, Salmonson T, Posch M, Vamvakas S, Hemmings R, et al. Gatekeepers and enablers: Hoe drug regulators respond to a challenging and changing environment by moving toward a proactive attitude. Clin Pharmacol Therapeut. 2013;93:425–32.
39. Vestergaard HT, D'Apote L, Schneider CK, Herberts C. The evolution of nonclinical regulatory science: advanced medicinal products as a paradigm. Mol Ther. 2013;21:1644–8.
40. European Commission: Regulation (EC) No. 1394/2007 on Advanced Therapy Medicinal Products. Summary of the Response to the Public Consultation. 2013b. Available at: http://ec.europa.eu/health/files/advtherapies/2013_05_pc_atmp/2013_04_03_pc_summary.pdf. Accessed November 2013.
41. House of Lords Science and Technology Committee. Regenerative Medicine Report. The Stationary Office, London. 2013. Available at: http://www.publications.parliament.uk/pa/ld201314/ldselect/ldsctech/23/23.pdf. Accessed November 2013.