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Proceedings: International Regulatory Considerations on Development Pathways for Cell Therapies

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ABSTRACT

Regenerative medicine is a rapidly evolving field that faces novel scientific and regulatory challenges. In September 2013, the International Workshop on Regulatory Pathways for Cell Therapies was convened to discuss the nature of these challenges and potential solutions and to highlight opportunities for potential convergence between different regulatory bodies that might assist the field's development. The workshop discussions generated potentially actionable steps in five main areas that could mitigate cell therapy development pathway risk and accelerate moving promising therapies to patients. These included the need for convergence of regulatory guidelines on donor eligibility and suitability of lines for use in clinical trials and subsequent commercialization for cell therapies to move forward on a global basis; the need to challenge and encourage investigators in the regenerative medicine field to share information and provide examples of comparability studies related to master cell banks; the need for convergence of guidelines across regulatory jurisdictions on requirements for tumorigenicity studies, based on particular cell types and on biodistribution studies; the need to increase transparency in sharing clinical trial information more broadly and disseminating results more rapidly; and the need to establish a forum for sharing the experiences of various approaches being developed to expedite regulatory approvals and access for patients to

innovative cell and regenerative therapies in the different regulatory jurisdictions and to assess their potential strengths and weaknesses.

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INTRODUCTION

The emergent field of regenerative medicine faces novel scientific and regulatory challenges. To assist field participants in understanding the nature of these challenges and to highlight opportunities that might assist the field's development, a group of representatives from funding and regulatory agencies, and investigators from companies and academia convened on September 17, 2013, in Bethesda, Maryland. They discussed challenges to and potential solutions for accelerating preclinical and clinical development of cell therapies and achieving multinational convergence of regulatory policies.

This international workshop, focused on the North American, European, and Japanese regulatory frameworks for developing cell-based therapies, had the following goals: (a) to provide product developer perspectives on the requirements for developing and delivering preclinical and early clinical trials, to identify areas where the regulatory approaches differ between regions, and to discuss the potential reasons for this; (b) to share regulatory perspectives on delivering preclinical and clinical trials in the U.S., Canada, the U.K. and Europe, and Japan, including expedited pathways for clinical development; and (c) to discuss needs and approaches to address the challenges in the field, including perspectives on the impact of future scientific advances and navigation of the development pathway. Regulatory guidances [1–11] and a recent workshop report [12] provided background context for this international workshop.

WORKSHOP PARTICIPANTS

Approximately 60 participants attended the workshop, including investigators from academia and industry; representatives from funding agencies and organizations supporting the development of regenerative medicine including the California Institute for Regenerative Medicine (CIRM), the Alliance for Regenerative Medicine, the U.K.'s Medical Research Council, Economic and Social Research Council, and Cell Therapy Catapult; and the Canadian Centre for Commercialization of Regenerative Medicine. Regulatory agencies represented at the workshop included the U.S. Food and Drug Administration (FDA), the U.K. Medicines and Healthcare Products Regulatory Agency (MHRA), the European Medicines Agency (EMA) Committee for Advanced Therapies (CAT), Health Canada, and the Japanese Ministry of Health, Labour, and Welfare (MHLW).

KEY FINDINGS

Through chaired sessions with participant presentations and floor discussion, the workshop sought to address questions relating to a number of the critical steps in the product development path for cell-based therapies. These include challenges that arise based on cell source/manufacturing, the value of preclinical animal models, the design of clinical trials, and the features of expedited clinical development and accelerated approval programs. The key findings from these presentations and discussions are provided below.

Cell Source/Manufacturing Regulation of Cell Types

Differences in current regulations covering cell sourcing and donor eligibility have created uncertainties regarding the suitability of different cells for clinical trials and commercialization, especially on a global scale. This is particularly critical for products derived from human embryonic stem cells (hESCs) that were not derived under current good manufacturing practice (cGMP) compliance, although they may have been banked under cGMP guidance, or derived prior to release of the latest FDA donor eligibility criteria.

Convergence of Guidelines

There is a need for convergence of guidelines among worldwide regulatory bodies, including cGMP requirements for cell sourcing and banking, particularly when GMP-grade materials may not be available.

Challenges

There are time-consuming and costly challenges for demonstrating comparability between multiple master cell banks (MCBs), especially for MCBs of limited size and lifespan. Additional regulatory guidance would be helpful; however, because these cell-based products have many complexities versus other biologics and limitations of the characterization methods make comparability a challenge, regulatory guidance alone will not suffice. Clear examples from investigators working in the regenerative medicine field would be of value.

Preclinical Animal Models

Small Versus Large Animal Models

The choice is influenced by a number of features unique to the cell-based therapy under development, including the clinical indication, the intended route of administration, whether a delivery device will be used, the range of cell doses to be tested, and whether immunosuppression will be required to support durability of engrafted cells or tissues. In some cases, multiple animal models may be required to test various aspects of product performance; however, in other programs, the availability of animal models may be limited.

Biodistribution

Technologies for assessing the pharmacokinetics and pharmacodynamics of cell-based therapies can be complicated and difficult to interpret. Imaging, for example, may lack sensitivity or require exogenous cell labeling. Biodistribution studies need to mimic the clinical route of administration and mode of delivery.

Testing Clinical Target Material Versus Analogous Model-Matched Material

The decision of whether to test the human clinical target material or model-matched cells in animal models (i.e., human or analogous porcine cells in a pig model) is guided by availability and predictability of the analogous animal cells and often is different among various product developers.

Tumorigenicity

For similar cell types, the recommended (or required) duration of in vivo tumorigenicity studies was 3 months for some countries and 6–9 months in others. Consensus on and harmonization among various countries of tumorigenicity study requirements for similar cell types would be most useful.

Potency Assay

Development of a potency assay is a complicated process and will be needed for lot release of the product in the phase III clinical trial and subsequently for the market. The assay must monitor the activity of the product in vitro in human cells and/or in animal models (as available). Efforts to identify and validate such an assay need to be initiated early in development. A suitable assay (which may not yet be validated but that demonstrates biological activity assay relevant to mechanism of action) may be required earlier for bank or lot release, manufacturing validation, and product-stability studies.

Defining Dose

Discussion among regulators suggested that they may be open to a number of paths of evidence, including allometric scaling based on animal studies, feasibility of dose preparation and delivery, or early clinical data from similar types of products.

Clinical Trials Registries and Manufacturing Resources

Resources exist, but a missing link is community-supported tools listing proof-of-principle and/or toxicity studies conducted for specific indications, cell types and doses, and/or routes of administration. Such a community-based database, keeping in mind the appropriate restrictions for maintaining confidentiality, would be a valuable tool.

Clinical Trials

Early Phase Clinical Trials

Early phase clinical trials, particularly first-in-human, emphasize evaluation of safety but also provide information on feasibility of administration and evidence of biologic activity. Careful consideration should be given to the various parameters influencing risk-benefit considerations, and early discussions should be held with regulatory authorities regarding the choice of a study population, the severity of disease, whether other therapeutic options exist, the doses to be used, the route of administration, the endpoints to be assessed, and the frequency and duration of those assessments. The risk-benefit considerations should be based on what is known about the product and guided by data obtained from the preclinical studies or other relevant clinical data from similar products.

Control Groups

Early phases of clinical development may benefit from the use of a control group to facilitate interpretation of safety data and provide a comparator for preliminary assessments of activity. Challenges remain in determining the best clinical control groups, reflecting ethical and practical considerations for blinding, and conducting sham procedures, particularly for cases in which surgical intervention is involved.

Approach

A stepwise protocol approach, with defined areas and triggers for adaption, is important to allow a smooth progression to the next cohort of patients and to accommodate clinical learning.

Comparable Materials

There is a critical need to demonstrate that the cellular material used in pivotal preclinical studies is comparable to that proposed for use in the clinical trial.

Training

To eliminate sources of variability and to ensure appropriate operator training, it will be important for participating surgeons to complete surgical training and qualification for clinical studies that include novel surgical techniques.

Accelerated Clinical Development and Approval Programs

International Cooperation

International cooperation in the area of cell therapies is imperative because, currently, different regulatory paths are being taken in different countries around the world.

Accelerated Mechanisms

Regulators are willing and already starting to explore accelerated mechanisms for regenerative medicine products, which should provide a stimulus for the industry; however, regulators are cautious about defining exactly how these mechanisms will be used in individual development programs. To accelerate the development and approval of cellular therapies, Japan has instituted a conditional adaptive licensing process. In the U.S., the existing “compassionate use” regulatory mechanism can be used to give patients access to investigational novel therapies; in addition, there are four expedited programs (fast track, breakthrough therapy designation, accelerated approval, and priority review designation). In the European Union (EU), supply of unlicensed medicines to meet specific needs of individual patients is possible through national implementation of named patient (“special” or compassionate use)

schemes and the hospital exemption (HE) scheme for advanced therapy medicinal products (ATMPs). In addition, accelerated licensing routes, including risk-based, conditional, and exceptional-circumstances licensing, are possible, and the adaptive licensing pilot is being advanced. In Canada, flexible regulations are in place to enable the evolution of new technologies. Accelerated licensing is supported by a Notice of Compliance with Conditions (NOC/c) policy. A new Orphan Drug regulatory framework is also under development.

Market Knowledge

The existence of different regulatory paths around the world raises the importance of early planning and regulatory advice that incorporates knowledge specific to the intended markets. If the ultimate goal is to develop a cell therapy product for global markets, it is important to plan and seek regulatory advice early (from the different regulatory authorities).

Regulatory Pathways

Existing regulatory pathways can be further refined or improved to help global development and make innovative cell therapy products available to patients in need.

SESSION FINDINGS

Cell Source/Manufacturing

The session was moderated by Mahendra Rao (NIH) and Maurice Wilkins (Imperial College London). The speakers included Paul Whiting (Neusentis, a Pfizer research unit), Melissa Carpenter (Carpenter Group Consulting), and Maria Trolliet (Organogenesis, Inc.).

Challenges With Current Regulations Covering Cell Sourcing and Donor Eligibility

Whiting spoke about the group's experience working with hESC-derived retinal pigmented epithelium as a cell therapy for the treatment of age-related macular degeneration. Whiting noted that there may be donor-eligibility issues in using therapies in the U.S. that were derived from non-U.S. cell lines. In particular, it was unclear whether the FDA guidance precluded the use of European-derived materials in the U.S. due to the perceived potential for transmissible spongiform encephalopathy (TSE) prion risk. Because there is no approved assay for TSE, the FDA may require different cell lines for material destined for use in the U.S., and this could be a major barrier to European companies performing clinical studies in the U.S. and, ultimately, commercializing the product.

Carpenter noted that the FDA donor eligibility guidance does not apply to tissue recovered before May 25, 2005, but it also does not specifically exempt this tissue from the requirement to comply. In addition to the challenges around working with non-U.S.-derived cell lines, the guidance raises the question of suitability of material sourced before this date and from a non-GMP environment such as in vitro fertilization clinics. The donor testing and screening required by this guidance is not currently consistent with hESC-derivation procedures. Examples were provided of hESC-derived cell therapies that had apparently not met the full donor eligibility requirements but had, to date, been able to enter early phase clinical trials in the U.S. It is unclear whether these cell lines will be suitable for licensure.

GMP Requirements for Cell Banking

Whiting and Carpenter also raised the issue of the timing for using good manufacturing practices throughout a product's life cycle. Some early cell lines now in the development pipeline were not derived under cGMP conditions but were banked under cGMP conditions. It was noted that although it is possible to apply to the FDA for an exemption, such an exemption is granted based on the specific product, clinical development stage, and clinical indication. This practice was identified as an area of uncertainty and risk for the development of cell-therapy products because the acceptability of a research-derived cell line for later stage clinical investigations and commercialization is still uncertain.

If the use of cell lines not derived under cGMP or not sourced from a U.S.-eligible donor is ultimately deemed unacceptable, then the possibility of changing cell source during the development pathway is raised and would require demonstration of product comparability.

Challenges for Demonstrating Comparability Between Multiple Clinical Lots and Master Cell Banks (Including Potency and Purity or Impurity Assays)

Carpenter spoke about the experience of one of the CIRM disease teams—the California Project to Cure Blindness—in producing multiple, small, clinical lots of hESC-derived retinal pigmented epithelial cells. This project uses expanded and differentiated cells that were cryopreserved at the progenitor stage such that demonstration of comparability will be required for the finished products manufactured from this intermediate product. Extensive testing of the cell bank and the final product was used to set final product testing and release criteria, and this knowledge will be used to demonstrate comparability. This pragmatic approach is suited to the product type; however, this strategy would be more difficult to use for a general cell source bank that may be used to make multiple different cell products.

Trollet provided illustrative cases from Organogenesis' experience with Apligraf and Gintuit product use and development to discuss the challenges and regulatory requirements for comparability of cell banks and lines. She addressed the point in the European guidance on comparability, which states that if a situation arises in which adequate comparability at the analytical and/or nonclinical level cannot be established, it must be demonstrated by clinical data. Due to large-scale production requirements, limited stability, and expansion potential, Organogenesis replaces cell lines and master cell banks on a regular basis. Consequently, Organogenesis has devised a strategy to demonstrate comparability by doing 1:1 comparisons of their newly manufactured cell lines against a reference cell line. For manufacturing the Apligraf product, each newly generated cell line is extensively characterized to demonstrate quality, safety, morphology, and function of the complex three-dimensional construct product to show comparability to a reference cell line already approved by the FDA.

Organogenesis recognized that it needed to replace its master cell bank on a regular basis. The comparability data from this extensive characterization work has been used to produce a change management protocol approved by the FDA for the introduction of new master cell banks. The acceptability of this approach in the EU via a type Ib variation route is currently being tested. This example represents another pragmatic approach for showing comparability. Comparability requirements have the potential to significantly affect the development of a product and, therefore, the company developing the product. Discussants felt it would be useful if more guidance using practical examples were available.

Preclinical Animal Studies

This session was moderated by Joy Cavagnaro (Access BIO) and Paula Salmikangas (CAT, EMA, the Finnish Medicines Agency [FIMEA]). The speakers included Jane Lebkowski (Asterias Biotherapeutics, Inc.), Kevin D'Amour (ViaCyte, Inc.), Bob Deans (Athersys, Inc.), and John Sinden (ReNeuron).

Choice of Animal Model, Biodistribution and Defining Clinical Dose

Lebkowski provided case examples describing the development of pluripotent stem cell-derived oligodendrocyte progenitor cells (OPCs) and cardiomyocytes (CMs). She noted that both programs required long-term persistence of cells for efficacy, but one involved local delivery and low doses (OPCs) for the spinal cord injury indication, whereas the other needed systemic delivery (potentially) and high doses for CMs in heart failure.

In the OPC program, a rat injury model was used because it demonstrated very similar pathology to that seen in injured humans. Assessments in the rodent included behavioral and functional outcome measures as well as the tumorigenicity, toxicology, and biodistribution of the cells. Doses from the rats were extrapolated to human doses for clinical trials. Large animal models were not used because they were either unavailable or uninformative due to the small study size of most nonhuman primate (NHP) models or the need to study minor (incomplete) injuries in NHP models.

In the CM program, more complex considerations guided selection of a model. For heart-failure programs, most groups use a combination of large and small animal models. The choice is dictated by heart rate incompatibilities with the cell product in some rodent models; the need for local delivery; variation in anatomy between species; and spontaneous arrhythmias, which can be typical in these models and further induced by inflammation. In these studies, biodistribution, tumorigenicity, and toxicology were assessed in small animals, and efficacy and biodistribution were examined in appropriate large animal models. It was found that studies with the proposed clinical product and delivery device were very difficult to conduct in pigs and other large animal xenograft models due to the high doses of immunosuppression required, which resulted in toxicities within 1 month. Rejection and inflammation occurred despite high immunosuppression doses, confounding the interpretation of arrhythmias. Thus, to obtain interpretable results, it was necessary to limit the duration of large animal studies.

D'Amour provided a case example from ViaCyte's work on VC-01, an hESC-derived, mixed population of pancreatic progenitors and endocrine cells that is macroencapsulated in a device intended to protect against immune attachment by the host and to provide a barrier to unwanted biodistribution. The device keeps the cells from migrating out of the capsule while allowing the distribution of insulin and other hormones. For efficacy studies, they used genetically immunocompromised mouse models because the macroencapsulation approach does not provide protection to xenografted cells. He emphasized that it was unnecessary to use diseased animals as a model for diabetes because mice are hyperglycemic compared with humans and can show a decrease in glucose levels after transplantation without streptozotocin treatment. In addition, human insulin-producing cell function is easily monitored via human-specific C-peptide measurement. The investigators used some streptozotocin-treated mouse models but only to demonstrate proof-of-concept for the efficacy studies, including verification of efficacy via product explant.

D'Amour explained that it was less valuable to define a dose based on cell number administered for their progenitor cell population because the implanted cells are proliferative and eventually cell numbers in the graft are largely dictated by the device size. In the mouse studies, the size of the device used produced "doses" of insulin-producing cell mass that were 30 times higher than the estimated therapeutic dose in humans, and the investigators still did not see hypoglycemia in the mice. Long-term persistence of cells up to a year is essential for product efficacy and has been demonstrated in immunocompromised mice. It was hard to justify using pharmacological immunosuppression because it was not clinically relevant as a result of the immunoprotective nature of the encapsulation device. The group demonstrated that undifferentiated hESCs are able to form teratomas that were contained in the device, but because the vasculature was prohibited from entering the device lumen, the teratomas were primarily composed of cartilage cells, which presumably developed in a hypoxic niche inside the expanding device lumen. Teratomas were not observed with the intended clinical product. The group conducted extensive testing of the device including carcinogenicity testing, device integrity, and pore-size stability (to confirm that no pore is bigger than the size of a cell).

Deans provided case examples using Athersys' proprietary multipotent progenitor cells (MAPCs). The investigators want to be able to use multiple cell banks in their trials and a traditional master cell bank/working cell bank (MCB/WCB) structure with well-characterized MCBs. To demonstrate comparability of the banks, they repeated a rodent study in a disease model with cells from the new bank and examined animals at 2–4 weeks after cell administration for toxicology endpoints and at 9–12 months after administration to evaluate efficacy and dosing. Deans highlighted that the group has had to work under different regulatory requirements for different territories and has designed the preclinical studies to meet the most stringent requirements of the different agencies (i.e., using the longest study duration required). Although Athersys has proposed the rationale that the MAPC product class has mechanisms that it can leverage across therapeutic areas, some regulatory agencies have not agreed with this approach and asked that each indication be developed as a completely new package.

Sinden provided case examples of two indications for which two different cell products were tested for treatment of critical limb ischemia and retinitis pigmentosa. In critical limb ischemia, the mechanisms of action include paracrine effects, angiogenesis, and muscle repair, which do not require persistence of the cells or immunosuppression. In this model, cells survived for approximately 7 days and did not appear to be affected by immune rejection. Using this model, the investigators were able to show dose dependency and tested the maximum feasible and therapeutic doses.

Sinden described that in retinitis pigmentosa, the mechanism of action includes trophic effects. The cells are given by local delivery, and immunosuppression is needed and long-term cell persistence is desired. They used a number

of models for this indication including a standard rodent model of vision loss (Royal College of Surgeon rats) for small animal dosing. They scaled dosing and delivery to pigs and used fluorescent microspheres to verify retinal coverage (which confirmed consistency of delivery in surgery). Verifying engraftment in rat knockout models ($\rho^{-/-}$) is possible but would require long-term immunosuppression to allow cells to survive and engraft.

Testing of Clinical Target Material Versus Analogous Animal Cells

Lebkowski highlighted that although analogous animal cardiomyocyte transplantation (i.e., transplanting pig cells into a laboratory pig) may have been useful for their heart failure program, the investigators were unable to differentiate cardiomyocytes from porcine induced pluripotent stem cells at sufficient purity to make this approach feasible.

Deans highlighted the following general approach for each therapeutic area: introduce cells into a disease model and try to get a disease-modifying signal; perform a dose-ranging study to optimize dosing; typically use analogous cells to identify activity and approximate dose and then match with human MAPCs; move into an animal model of the human delivery system (which may or may not be a disease/injury model) and then into a large animal disease model, typically in compliance with good laboratory practices. This approach has been successful in identifying optimal dosing that has held up in a clinical trial.

Sinden described how, for longer term studies of a retinitis pigmentosa indication, investigators used human cells and also looked at the analogous product (porcine allograft) in a pig model with matched doses and procedures.

Potency Assays

Deans highlighted extensive work on developing and validating potency assays. His team has screened for angiogenic factors with activities that correlate in in vitro and in vivo assays, inhibited activity in vitro using antibodies, and then added the factors back to show restoration of function in a vessel formation assay. Using proteomic approaches, the investigators validated that three factors were needed to ensure patent vessel formation; otherwise, poor or leaky vessels were formed. They have used these potency assays for more than 17 different manufacturing campaigns. Deans indicated that he and his colleagues are developing a panel of potency assays reflecting critical product attributes with the understanding from regulatory agencies that potency testing would be indication specific, and appropriate assays for each indication would be selected from the panel.

Clinical Studies

The session was moderated by Ellen Feigal (CIRM) and Elaine Godfrey (MHRA). The speakers included Paul Williamson (Janssen Research and Development, LLC), Geoff Symonds (Calimmune, Inc.), and Nick Boullis (Emory University).

Differences Between Cell Therapy and Traditional Clinical Trials

Williamson noted that execution of cell therapy clinical trials often requires that organizations adapt and adopt new procedures compared with those used for traditional clinical trials to support a biologic. He highlighted, for example, the key importance of trial sponsor involvement in the donor eligibility process and the importance of interpreting those records and any observed adverse events with a high level of scrutiny and vigilance. He also noted the example of a clinical trial in which the final cell processing occurred at the cell processing center at the clinical institution where the subject was treated, and the batch record sign-off took place after a day 14 sterility test and after the patient had been dosed. To complete a batch record 14 days after a subject is treated in a clinical trial is vastly different than signing off immediately after manufacture and before dosing, which most large organizations conducting clinical trials are accustomed to doing. New procedures will be required to accommodate such differences.

Williamson also highlighted challenges in cellular therapeutics related to interpreting preclinical data to inform the development of clinical protocols and risk assessment. Williamson noted that preclinical testing using analogous animal cell products, although potentially useful in some situations, can be misleading. Often the mechanisms of action, immunogenicity, dose size, biodistribution, persistence, and targeted delivery (e.g., due to physical size of

cells or size of the compartment into which the cells are delivered) may differ from the clinical product and the clinical state.

Importance of Refinement and Validation of Surgical Techniques

Conventional surgical procedures may not be sufficient for surgical administration of cell products. Many cell therapy products require a surgical procedure for cell delivery, creating a major source of variability or potential failure of a clinical protocol not due to the cell therapy product itself. Williamson gave the example, observed by his team, of retinal blebs made for subretinal delivery that did not self-seal immediately, potentially allowing an unintended distribution route of cell egress into the vitreal space. This surgical observation sent the team back to the preclinical development phase to make a microcatheter for optimized delivery and to devise a new surgical delivery technique.

Boulis noted that it is important to control the quality of surgery and administration techniques through surgeon training and observation, which he combines with a training video showing administration of the cell therapy and postoperative vessel anatomy, to indicate where the cells are expected to be located during histological tracing and identification. One has to consider whether a separate investigational drug exemption is needed for a delivery device used during cell administration. Boulis advised early interaction with the FDA and noted that if the FDA decides to regulate the delivery device and cells as a combination product, then the device may not necessarily be allowed for use in other indications, although the preclinical packages and surgical training techniques may be relevant.

Determining Risk-Benefit Ratio and Duration of Follow-Up

Williamson emphasized that conventional approaches to pharmacokinetics are not transferable to cell therapy trials. Specifically, the duration of follow-up to assess safety and washout of the investigational products based on half-lives of pharmaceuticals are not relevant in situations where cells persist within the body following transplantation. Consequently, the question of how long safety follow-up should be monitored is challenging. In some cases, this can be informed by data obtained from preclinical models; however, xenografts of the clinical investigative cell-based product derived from a human donor, administered in animal models, can be misleading in this regard.

Williamson pointed out ethical difficulties in early clinical trials using cell therapies involving surgical delivery in cases where placebo or sham controls are proposed. Alternatively, historical controls, parallel standard of care groups, or modified sham procedures such as using a needle hub mark to simulate surgery may be more ethically sound for determining a treatment-related effect.

Symonds described Calimmune's clinical development of a therapeutic approach to circumvent HIV entry. The approach involves gene-engineered modification of autologous T cells and hematopoietic stem cells. Calimmune is currently conducting and planning clinical trials in the U.S. and Australia, enrolling patients with HIV/AIDS. In describing the preclinical development pathway for this investigational approach, he pointed out that the company was able to leverage some of the discussions and work it had done in Australia during presentations to the FDA such that it was unnecessary to repeat the preclinical work for the U.S. Investigational New Drug application (IND). He also described the similarities between the regulatory pathways of the Australian Therapeutic Goods Administration and the FDA that made this leveraging possible.

Boulis summarized the rationale for his trial design to test fetal-derived cell therapy in central nervous system diseases. Among the design features he evaluated were combined therapy and multiple dimensions of risk, such as number and volume of injections, rate of injections, and severity of neurological deficit affecting the patient population. He also noted that enrollment requirements for assessing chronic disease progression are distinct from those for assessing progression following acute trauma. Cross-over designs can be considered but may be unfeasible in rapidly progressing disease settings. In choosing the patient population for clinical trial enrollment, the FDA uses a risk-based approach. One approach is to use the concept of risk escalation in designing the clinical development plan, for example, starting at the lower end of the spinal cord and moving up because adverse events that could occur at lower levels of the spinal cord would likely have less patient impact than those that could occur at higher levels, providing a more conservative administration route before escalating to surgical sites that may involve a higher degree of risk. In terms of safety considerations, there are differences between the perspectives of the U.S. and EU regulatory agencies, but they share the view that safety of the delivery procedure will be considered in the

context of the ultimate risk-benefit analysis. Boulis emphasized that it is critical to begin planning for the clinical trial as early as possible based on an understanding of the product and its mechanism of action.

Accelerated Regulatory Programs

The session was moderated by Natalie Mount (Cell Therapy Catapult) and Kathy Tsokas (Janssen). The regulators from the FDA, EMA, Health Canada, and MHLW described the current regulatory mechanisms for regenerative medicine in each country or region. Speakers included Celia Witten (Center for Biologics, Evaluation, and Research [CBER] Office of Cellular, Tissue and Gene Therapies, FDA), Paula Salmikangas (CAT, EMA, FIMEA), Peter Ganz (Health Canada), Yuji Arakawa (MHLW), Malin Nittve (Karolinska University), Alison Wilson (CellData Services), and Maria Pascual (TiGenix). The purpose of this session was to discuss regulatory issues and share thoughts and experiences to help promote global regulatory convergence and accelerated development mechanisms.

U.S.

Witten provided an update on programs in the U.S. under the oversight of the FDA. There has been a steady increase in cell and gene therapy regulatory submissions: in 2012, there were 100 new IND submissions for cell therapy products and 50 new IND submissions for gene therapy products.

Currently, there are four expedited programs: fast track, breakthrough therapy designation, accelerated approval (approval can be based on a surrogate endpoint that is predictive of clinical benefit), and priority review designation. The breakthrough therapy designation is a newly created expedited program under the FDA Safety and Innovation Act. As of May 31, 2013, the FDA (CBER and the Center for Drug Evaluation and Research [CDER]) had received 59 breakthrough therapy designation requests, with 20 requests granted and 20 requests denied. At the time of the workshop, there had not been a cell or gene therapy product designated as a breakthrough therapy.

Postmeeting Note.

At the time of this International Workshop in September 2013, the breakthrough therapy designation was newly instituted. As of April 18, 2014, CDER had received 150 requests, with 42 requests granted and 72 denied; as of March 31, 2014, CBER had received 28 requests, with 2 requests granted and 20 denied [13]. As of April 10, 2014, the first gene therapy product was designated as breakthrough therapy [14]. CBER representatives have presented on the breakthrough therapy designation and have indicated the high bar for clinical evidence that is required to designate a cellular or gene therapy as breakthrough.

EU

Salmikangas gave a comprehensive overview of the ATMP regulatory framework of the EU, the evolving landscape in relation to the centralized procedure versus regulations in each member state, and the transition to ATMP regulation for products that were previously legal on national markets via the GMP certificate but went through a transitional period that ended December 2012.

With regard to accelerated development, if certain specific conditions are met (e.g., life threatening or highly debilitating conditions), the EMA can grant conditional marketing authorization or marketing authorization under exceptional circumstances. In addition, the ATMP regulation foresees a risk-based approach with possibilities for postmarketing safety and efficacy studies for all ATMPs; however, the benefits and risks still must be positive at the time of marketing authorization. Glybera is an example of an ATMP that has marketing authorization under exceptional circumstances.

Hospital exemption under Article 28 1394/2007/EC is a unique EU regulatory mechanism that allows an exemption to the regulatory requirements set in Directive 2001/83/EC; however, medicinal product requirements still apply (e.g., traceability, quality, pharmacovigilance). HE can be applied for an ATMP that is prepared on a nonroutine basis, in a hospital, under the responsibility of a medical practitioner, to meet the needs of an individual patient.

Salmikangas also described the adaptive licensing regulatory mechanism that is currently under discussion at EMA and that allows for prospective, iterative phases of evidence gathering. Although EMA has mapped out the next

steps to further advance adaptive licensing, including five retrospective case studies, questions and concerns remain surrounding this new regulatory mechanism.

Postmeeting Note.

Since this meeting was held, there have been several relevant developments of note in the EU: publication of the summary report of the consultation on the 5-year review of the ATMP regulation [15]; call for companies to participate in the adaptive licensing pilot [16]; and launch of the U.K. (MHRA) early access scheme to accelerate access to unlicensed medicines for patients who suffer from life-threatening or seriously debilitating conditions when there is a clear unmet medical need [17].

Canada

Ganz discussed how advanced cell therapy and gene therapy products are regulated under the Food and Drugs Act and Regulations in Canada. These regulations allow the application of a risk-benefit approach to all drug regulatory processes and are sufficiently flexible to enable the development of novel products. There are also accelerated pathways that can be applied to cell therapy and gene therapy development. The priority review designation, for example, can reduce review time for market approval from 300 to 180 days. There is also a policy to allow NOC/c and an orphan drug framework that is currently under development. Products that obtain market access through these pathways are subject to stringent postmarket surveillance conditions that allow adequate monitoring of safety and efficacy, similar to the progressive licensing in the EMA.

In addition, there is a special access program for Canadian physicians that allows the compassionate use of unlicensed therapies in the absence of other treatment options; this is not intended to support market application.

In light of the many uncertainties of cell therapy use, particularly with regard to safety, Ganz emphasized the importance of the fundamental regulatory requirements for ensuring safety, effectiveness, and quality of any therapeutic product. In order to inform and assist sponsors, Health Canada is currently working on a guidance document that outlines the quality, preclinical, and clinical expectations for premarket evaluation of advanced cell therapy products. These would include all products considered ATMPs by the EMA, with the exception of gene therapy products.

Japan

Arakawa provided an update on regulations in Japan. He noted two approved cell therapy products and four clinical trials under the Pharmaceutical Affairs Law (PAL). In order to advance stem cell research and regenerative medicine development, Japan has proposed amendments to the PAL to strengthen safety measures for drugs, medical devices, and other regulated products. The amendments are also intended to establish well-suited regulation for regenerative medicine, considering the unique characteristics of such products. Under the proposed amendments, a new definition of regenerative and cellular therapeutic products is set apart from pharmaceuticals and medical devices in the PAL. For this new category of products, a tentative approval will be introduced as adaptive licensing with condition (confirmation of probable benefit and safety) and with postmarket commitments to confirm efficacy and safety for full marketing. It is anticipated that this new regulatory mechanism could shorten the current approval system by approximately 3 years. As a postscript to this international workshop, the Act on the Safety of Regenerative Medicine and the Revised Pharmaceutical Affairs Law were simultaneously passed by the Japan Diet in November 2013 and will come into force within 1 year [18].

In addition to speakers representing regulatory agencies in various countries, the second part of the session included three speakers from the regenerative medicine community who described their experiences in developing cell therapy products and the challenges of addressing regulatory requirements from different regions.

Karolinska University Hospital

Nittve described her experiences working in the Karolinska University Hospital in Sweden and noted the gap between cell therapy research and implementation in a hospital environment, with a focus on hospital exemption. As discussed earlier, the ATMP regulation gives member states the power to authorize the use of custom-made ATMPs prepared on a nonroutine basis in the absence of a marketing authorization, provided that the product is used for individual patients in a hospital and under the professional responsibility of a medical practitioner. The HE enables

patients to receive an ATMP under controlled conditions in cases for which no authorized medicinal product is available. In addition, it facilitates research and development of advanced therapies by nonprofit organizations (e.g., academic institutions and hospitals), and it can be a valuable tool for hospital researchers to obtain information prior to formal clinical trials and seeking marketing authorization.

Oversight of HE resides with national competent authorities, and their varied requirements for implementation have previously been identified as a concern. These varied requirements present challenges for using HE data to support further product development. Nittve recommended that all stakeholders work together to refine HE with the goal of making therapies available for patients in need.

Organogenesis

Wilson discussed the Organogenesis products Apligraf and Gintuit as case studies to illustrate the challenges companies face when dealing with the different regulatory considerations of U.S. and European regulatory authorities. Organogenesis has 15 years of experience and has shipped approximately 625,000 products. Wilson presented examples of differences in standards across different regions regulated by different agencies. In particular, she noted variations in cell source/manufacturing and GMP requirements, such as product and cell bank characterization, comparability packages, and uncertainties in determining whether clinical data generated in one region are adequate to address questions by regulators from another region. She highlighted Gintuit as an example in which, in the 1990s, the EMA raised questions about the suitability of cell culture materials and acceptability of clinical data (obtained with a product that was different from current manufacturing practices), although a BLA had been approved by FDA CBER.

Wilson also noted that a guideline on a risk-based approach for ATMPs was released in February 2013. It may represent an opportunity to accelerate development of products approved in one region for introduction in another region; however, the approach excludes the use of pre-existing clinical experience. Consequently, it is unclear how much data would be considered adequate and how much clinical data should be collected prospectively or collected after market. Further details on specific mechanisms in the risk-based approach need to be worked out to be truly helpful to accelerate global development.

TiGenix

Pascual discussed the experience of TiGenix, a company with one autologous product on the market (ChondroCelect, approved in 2009) and several allogeneic candidates in the pipeline. She shared the company's challenges, particularly regulatory challenges, in developing cell therapy products. These include the challenges in trying to adhere to guidelines that are still under revision, unclear expectations, and the difficulties in advancing cell products in a regulatory environment in which both sponsors and regulators are still learning. In order to formulate a "global" development plan to achieve approval across regions, she proposed a strategy of "progressive" global product development that would require accelerated and integrated pathways and acceptance of global clinical and cell source/manufacturing data. She also stressed the need for harmonization of accelerated procedures so they can be used in global development. With regard to HE, Pascual noted that, in her opinion, the HE is not the best way to address patients' needs uniformly across the EU because it could potentially lead to medical tourism; therefore, treating patients through HE should no longer be allowed when a fully validated, centrally approved ATMP is available.

PERSPECTIVES AND POTENTIAL NEXT STEPS

The workshop discussions generated potentially actionable steps in five main areas that could mitigate cell therapy development-pathway risk and accelerate moving promising therapies to patients.

First, for cell therapies to move forward on a global basis, there needs to be convergence of regulatory guidelines on cell donor eligibility and suitability of cell lines for use in clinical trials and subsequent commercialization. With regard to regulation of cell lines for therapeutic development, a great degree of ambiguity currently surrounds the use of cell lines derived from donors prior to the year 2005—ambiguity for which there is little scientific basis. In the view of many of the workshop participants, if a regulatory authority approves a particular cell line for use for a first-in-human clinical trial for a specific disease indication at a specific stage in disease progression, the regulatory

authority should provide assurance that this cell line can be used for subsequent commercialization. If there is a need to change the cell line during clinical development, consideration of comparability requirements should be undertaken.

Second, investigators in the regenerative medicine field should be challenged and encouraged to share information and provide examples of comparability studies as they relate to master cell banks. Efforts, for example, are under way to develop consensus-based reference cell materials for mesenchymal stromal cells to facilitate inter- and intralaboratory comparisons [19, 20].

Third, there should be a convergence of guidelines across regulatory jurisdictions on requirements for tumorigenicity studies based on particular cell types, as well as on biodistribution studies. One way to facilitate and expedite such a process may be through the creation of a community database through which information could be collected on standards, assays, and methods guiding the types of animal and in vitro models to use and protocol designs for such studies. Importantly, assessment of potential tumorigenic risk is needed prior to using a particular cell type in first-in-human trials.

Fourth, clinical trials are a complex and expensive endeavor; therefore, more transparency and broad sharing of information are needed, as is more rapid dissemination of clinical trial results and data. An effective infrastructure for the aggregation, analysis, and dissemination of clinical trial data could serve to accelerate rigorous testing and development of safe and effective therapies, empower patients and the public to make informed decisions about research participation, and engage the broader community through shared knowledge and resources to accelerate medical innovation and clinical research.

Fifth, within the different regulatory jurisdictions discussed, various approaches are being developed to expedite access for patients to enroll in innovative cell and regenerative therapies. In the U.S., qualified accelerated access programs are general in scope and are not geared toward specific technologies. In Canada, general accelerated access programs consist of the NOC/c policy, which was used to provide conditional approval for Prochymal in 2012, and a soon-to-be-released orphan drug framework. In the EU, the EMA has implemented a provision for accelerated routes including licensing under exceptional circumstances, risk-based assessment for ATMPs, and conditional licensing and recently launched an adaptive licensing pilot. In Japan, there is a national focus on an accelerated pathway for regenerative and cellular therapeutics. A forum for sharing the experiences with these different approaches and assessing their potential strengths and weaknesses would benefit stakeholders globally.

AUTHOR CONTRIBUTIONS

E.G.F., J.P., and N.M.: conception and design, collection and/or assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript; K.T., S.V., and J.Z.: collection and/or assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript; C.P.: collection and/or assembly of data, manuscript writing, final approval of manuscript.

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