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PERSPECTIVES

Progressive Approval: A Proposal for a New Regulatory Pathway for Regenerative Medicine

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SUMMARY

To stimulate a broad discussion between academics, practicing physicians, corporate managers, and members of the regulatory community, we describe a proposal for a new regulatory pathway for human cell- and tissue-based products. The new components of the pathway are intended to accelerate patient access to a wide array of novel therapeutics, strengthen R&D infrastructure, and expand patient numbers and timelines for efficacy testing through a transparent and publicly accessible website for real-time reporting of outcome data and 5- to 10-year, long-term follow-up. STEM CELLS TRANSLATIONAL MEDICINE *2014;3:560–563*

INTRODUCTION

There is a growing perception in the regenerative medicine community that 20th century regulatory policies are not necessarily well suited for 21st century human cell- and tissue-based products (HCT/Ps). Of particular concern is the fact that many HCT/Ps currently in development are intended to be long-term or permanent grafts whose performance could change over time frames exceeding those currently used in most clinical trials. Also, as a practical matter, the United States and numerous other countries are facing an imminent rise in chronic degenerative diseases because of an aging population that will place enormous economic and personal pressures to accelerate access to regenerative therapy. In consideration of these and other factors, we offer a proposal to stimulate broader discussion of possible alternative regulatory pathways. The goal is to provide a practical means of funding long-term patient monitoring while simultaneously accelerating the pace of access to new products. We state up front that we are both opinionated and conflicted, reflecting academic as well as industry perspectives. We offer this proposal in the hope that new regulatory procedures including newly articulated "risk-benefit" approaches can be delineated to take the field down a progressive yet safe and practical path.

BACKGROUND AND RATIONALE

Regenerative medicine is an emerging discipline on the frontiers of medical science with the potential of restoring function in a large number of tissues compromised by incurable and degenerative diseases. These advances are creating products that not only have the potential to eliminate disease, but also to restore normal tissue function. They therefore have the potential for a profound impact not only on *quality* of health care, but also on its *economics*. Two examples: laboratory experiments and initial clinical trials using stem or medicinal cells have provided evidence for the newfound ability to restore cardiac muscle after a myocardial infarction and to restore function to a kidney destroyed by chronic renal disease. Numerous lives will be changed and prolonged and hundreds of millions of health care dollars will be saved if and when these cell-based therapies are made available to patients in a timely fashion.

The foundation of this revolution in medicine is based on new discoveries in adult progenitor and pluripotent stem cells. Collectively, these cells have the ability to "branch" or differentiate into all cell types in the human body and, therefore, offer strategies to potentially provide a wide array of therapeutic effects at tissue sites of disease for the first time in history. Regenerative medicine is therefore considered to be a platform technology allowing the incorporation of diverse disciplines in science such as molecular strategies to generate novel genetically modified cells, bioengineering to incorporate defined matrices for improved engraftment of the cells, and combination products wherein cells and matrices are combined with specific growth factors. Therefore, from numerous perspectives, regenerative medicine is unique in nature and potential for development into clinically relevant therapeutics. A new cornerstone logic is the recognition that in individuals of any age, there is an innate tissue-level regenerative potential that can be harnessed to self-repair damage.

This unique nature of regenerative medicine and the novel products being provided do not lend themselves to traditional regulatory processes for ascertaining risk and benefit. Thus, there is an unacceptable delay in providing these novel and more effective solutions to patients with concomitant monetary savings to the health care system. This is particularly relevant given that we are just now seeing the advent of the tsunami of health care costs associated with the 76 million people-strong baby boom generation. Age-related degenerative diseases, common to most of this cohort, are the single largest driver of the unsustainable costs of

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Medicare. Therefore, any delay in implementing new technologies that can alleviate human suffering and simultaneously reduce costs will not only adversely affect our fellow citizens, but also will discourage investors from funding research and development opportunities in regenerative medicine for the next generation.

To address this problem, we propose creating a unique regulatory pathway that can speed approval without sacrificing safeguards for patient safety. A pilot project that will establish proof of principle could focus only on mesenchymal stem cells (MSCs) or clonally defined pluripotent stem cell-derived embryonic progenitor cells. The latter cells are derived from pluripotent stem cells, but because they are clonally expanded downstream of pluripotency have, in our opinion, essentially no known risk of generating uncontrolled teratomas following engraftment. Regulators involved in oversight of this pilot project should work closely with experts (perhaps creating a new regenerative medicine panel) with detailed knowledge of stem cell biology and the production of regenerative medicine constructs to define the types of products that qualify for this pathway to approval.

The New Regulatory Pathway

The pathway will include two steps. The first will focus on establishing product safety. It will involve a premarket assessment of the preclinical data, proposed mechanism of action, and scientific rationale for the expected therapeutic benefit. In addition to this preclinical assessment, the first phase will require carefully designed and executed clinical trials in human subjects to establish product safety as determined by absence of severe adverse outcomes (comparable to the current phase I trials). Once safety (i.e., absence of toxicity and presence of relevant efficacy as is sometimes obtained in phase I or phase I/II trials) is established, the product can be approved for market-determined payment under a protocol accepted by the regulatory authority to establish the efficacy of the treatment in a postmarket (i.e., phase IV) setting. Such product payments by insurance and governmental agencies are key to the success of this proposal and must be sufficient to fund the long-term follow-up.

It may be that special medical expertise and credentialing will be required to administer the product to the patient and, perhaps, to propose the "proper" dosing (this is now the case in Japan, for example). This phase incrementally establishes efficacy by using a web-based data management system that, in real time, acquires and analyzes information on a daily basis from both physician and patient. This proposed regulatory pathway differs from the current traditional regulatory scheme in that once the phase I clinical trial has established safety, the cumbersome and costly phase II and phase III clinical trials usually conducted on very small populations of patients and under highly artificial conditions are avoided. Instead, the phase II and III trials are replaced by a large population postmarket study that captures, in real time, the full experience of a large population. Lastly, we propose that a 5- to 10-year follow-up be established to ensure the long-term safety of these innovative treatments. Again, the follow-up data will be entered in real time on the publicly accessible website that protects the patient's identity. Parenthetically, we suggest that this altered approach could be consistent with the recently adopted guideline document "Risk Evaluation and Mitigation Strategies" (FDA).

The goal of the proposal is to establish an efficient, scientific, and evidence-based regulatory pathway that will more rapidly deliver these novel, potentially lifesaving, and health-enhancing products to patients using regulated protocols. The regulatory agency will have full authority over the assessment of preclinical and clinical data that establish the safety profile of the product when used according to prescribed methodology by qualified physicians. Once the regulatory agency determines the level of anticipated risk, the product will be "progressively" approved and registered for marketing for widespread use under carefully monitored and strictly enforced guidelines. The sponsor and regulatory agency together will be the repository of data submitted electronically by the treating physician as well as the individual patient on a prescribed schedule. The data will be continuously analyzed and results will be reported on an ongoing fashion to all investigators involved in the study. In this context, perhaps a progressive diminution of the placebo controls (and/or the exclusive use of historical clinical data) can also be built into the analysis to provide the broadest access to these new therapeutics. Clearly, evidence-based assessment of clinical outcomes requires random, blinded, placebo-controlled procedures and outcome studies. However, ongoing statistical analysis, in real time, could allow the diminution of eventual elimination of the placebo controls when the efficacy reaches statistical significance. The regulatory authority will use such data analysis to make modifications to its guidelines for clinical use or, if required, remove the product from clinical use. Because such analysis is on a publically accessible website, all conclusions, deliberations, and notifications will be seen, and comments from the community at large will add value to the process.

Upon acquisition of sufficient data on which a definitive regulatory decision can be made, the regulatory agency can make a conclusive regulatory determination including labeling for widespread unmonitored usage.

By eliminating costly, time-consuming, and often inadequate traditional phase II and phase III clinical trials, the proposed process will (a) rapidly and safely bring innovative complex products to patients; (b) create a regulatory pathway involving only two steps to fulfill the mandate to establish safety and efficacy of the product when used as directed; (c) provide a long-term follow-up under complete transparency and at the option of the regulatory agency with public, medical, and scientific oversight; and (d) because the product would be "approved," the vendor could experience a substantial cash flow, which itself would decrease its dependency on uncertain and often inadequate investment and commercial partnerships.

Proposal

Eligibility

Progressive approval should be available for a new therapy intended to provide a meaningful advancement in the treatment of serious or life-threatening disease, which offers the promise of one or more of the following:

- Approved therapy for a condition or targeted subpopulation with the recognized medical condition.
- Ability to treat patients unresponsive to, or intolerant of, existing approved therapies. Importantly, such treatments may be first-line opportunities with newly diagnosed patients. Failure to respond to all known therapies need not be a precondition. For example, if the sponsor has preclinical data or phase I safety and efficacy data that it can affect the progression of multiple sclerosis (MS), why should the studies be on end-stage or drug-unresponsive patients? If newly diagnosed patients have

a choice of a new, cell-based therapy or standard drug-based therapy, it may be a choice between temporary stasis versus curative technologies. This is, indeed, the promise of regenerative medicine.
- Ability to treat rare diseases or disease subpopulations based on biomarkers or genetics (e.g., personalized medicine), again, perhaps as a first-time therapy.
- Ability to offer a significant improvement in outcomes for patients compared with existing approved therapies, either alone or in combination with existing approved therapies. Improvement in outcomes may reflect improved efficacy, improved safety, or an enhanced balance of efficacy and safety, compared with existing approved therapies.

Process for Eligibility and Designation Decisions

The sponsor could apply for treatment under progressive approval guidelines before or any time after a pre-Investigational New Drug (IND) meeting. Whether a therapy should be considered for or the subject of progressive approval should be the option of the sponsor. But the regulatory authority makes the final determination as to whether the therapy meets the qualification criteria for progressive approval. A decision that the product is not eligible should not preclude a subsequent decision based on new information that the product should be considered eligible for progressive approval.

Standard for Progressive Approval

Marketing approval should be granted in the following cases:

- In general, approval should be granted at the earliest possible time when the available evidence suggests that the therapy is more likely than not to provide a favorable benefit-risk tradeoff to its intended patient population.
- For example, progressive approval may typically be granted following completion of one phase I trial, provided that the available preclinical and clinical evidence suggests a favorable benefit-risk tradeoff.
- It may also be granted earlier if the regulatory authority deems that the benefits of immediate availability of the therapy outweigh its risks for the intended population.
- Approval should be conditioned on written agreement between the regulatory authority and the sponsor regarding plans designed to establish the postmarket infrastructure for selection of qualified physicians to administer the therapy, the infrastructure for physician and patient data acquisition, and ongoing analysis and dissemination of the data by the regulatory authority and sponsor to all participants in postmarket administration of the therapy.
- The sponsor must bear all costs including a fee to use the regulatory agency website portal for data management for all aspects of the trials until the agency grants final approval.

Expiration and Renewal

Progressive approval should remain in effect unless and until the regulatory authority determines that the conditions for progressive approval (i.e., that the available evidence suggests that the therapy is more likely than not to provide a favorable benefit-risk balance no longer apply, as described under Withdrawal of Approval). The holders of INDs and Biologics License Applications approved via progressive approval should submit supplements to convert their products to full approval when they have gathered the data needed for that approval.

Postmarket Restrictions

Postmarketing reporting requirements must be stringently adhered to (i.e., recordkeeping and safety reporting). The regulatory authority may insist on use of all available tools, including Risk Evaluation and Mitigation Strategies, postmarket surveillance, controlled distribution, physician training, credentialing and registries, and so forth, to ensure a favorable benefit-risk balance in the postmarket.

Of importance to the progressive approval program is the commitment of the sponsor to long-term follow-up in the range of 5 to 10 years. The details of what will be reported and analyzed will be agreed on by the sponsor and the regulatory agency and posted on the portal of the publically accessible website. Should an adverse event occur, the entire medical and scientific community will observe this on the website and could provide expertise to help understand the course of this event.

Withdrawal of Approval

Withdrawal of approval (with an opportunity for a postwithdrawal hearing) should occur in the event that the regulatory authority concludes that it is no longer likely that the benefits of the product outweigh its risks or if the sponsor and treating physicians have not complied with timely submission of clinical data.

The sponsor will be required to submit a report to the regulatory agency once every 3 to 6 months on the status of the product until full approval is obtained or progressive approval is revoked. This report will provide an update on the progress of the agreed-on development program toward full approval; will update all available evidence regarding the efficacy and safety of the therapy in the approved indication and population; and will provide an updated assessment of the benefit-risk balance based on all available evidence at that time.

Following submission of each such report, the regulatory authority will conduct a review of the product's progressive approval status. It may electronically involve or convene an advisory committee (tailored with expertise in regenerative medicine) in conjunction with such a review. If the authority concludes that it is unlikely that the benefits of the product outweigh its risks in the intended population, then it may initiate withdrawal procedures.

Labeling and Promotion

The package insert of a progressively approved therapy should disclose its status. Marketing and promotional claims should be permitted, in accordance with the product label, in the same manner as with therapies granted full approval.

Charging and Reimbursement

Therapies approved under this pathway should not considered investigational; thus, they are subject to the same coverage and reimbursement policies applicable to therapies approved under the traditional process.

- This proposal depends heavily on a well-established infrastructure of electronic medical records as well as a reliable network of monitoring and reporting of product performance in real time. This regulatory pathway is based on dynamic real-time assessment rather than static snapshot measures of

performance inherent in the prescribed follow-up protocols of the traditional phase II and phase III clinical trials. There must be well-described patient selection parameters, a universal protocol for acquisition of clinical and laboratory data, and parameters for determination of response to therapy.

- Upon conclusion of the phase I or "safety" protocol, all data will be submitted by the sponsor to the regulatory authority to obtain approval of the safety profile and approval for the therapy to be considered for the phase IV portion of the study. This will include approval of the procedures for patient eligibility and selection, and approval of treating physicians and the methodology for data acquisition and reporting. All physicians wishing to administer the therapy must certify their adherence to prescribed indications and to treatment protocols.
- A single web-based portal for data acquisition and monitoring will be created by the regulatory agency and financially supported by the sponsor. The regulatory agency will have unlimited and complete access to and control of the portal for purposes of monitoring compliance to patient selection and treatment parameters as well as detection of unexpected adverse outcomes.
- Data will be aggregated and disseminated by the sponsor in real time to the regulatory authority and participating physicians with periodic summary reports as prescribed. The regulatory agency may open this portal to the public to allow the broadest access and transparency possible while protecting patient identity.

Example of Pending Adult Stem Cell Therapies

A type of cell isolated from adults called mesenchymal stem cells, believed to be a type of vascular pericyte, shows great promise in medicine. When MSCs are infused into the circulation, they can in certain cases home to injured tissue and produce a variety of bioactive molecules that protect the injured tissue from overly aggressive inflammatory and degenerative processes. Two examples are as follows: Within 48 hours of an acute myocardial infarct (AMI) or heart attack, allogeneic MSCs are infused into the patient, with the result being improved cardiac performance. A substantial number of MS patients in an open-label trial were infused with MSCs with substantial regenerative effects. In animal models of MS, the infused human MSCs are apparently not immediately recognized by the animals' immune system, and these MSCs appear to home to the damaged central nervous system and slow the destruction of the animals' myelin around nerves. The MSCs are suggested to further cause the brain's neural stem cells to differentiate into myelin-wrapping oligodendrocytes and, thus, impart a therapeutic effect in the animal model.

In total, in a variety of clinical trials, allogeneic and/or autologous human MSCs have been infused into 20,000 to 50,000 people with few if any adverse events. These MSCs are now being tested in humans with MS, amyotrophic lateral sclerosis, Crohn's disease, rheumatoid arthritis and osteoarthritis, AMI, juvenile diabetes, stroke, spinal cord cuts or contusions, sepsis, and a large variety of other clinical indications. More than 380 clinical trials are in play when the http://clinicaltrials.gov website was searched using "mesenchymal stem cells"; about 200 were active on December 1, 2013.

Examples of Pending Embryonic Stem Cell Therapies

Embryonic stem (ES) cells were first isolated in 1998 and have the potential of becoming all somatic cell types. As a result, the potential range of products from embryonic stem cells is vastly larger than that from adult stem cells, but also, by necessity, these products are at an earlier stage of development. Geron Corporation was the first to initiate a phase I trial for the use of human ES cell-derived oligodendrocyte progenitors to remyelinate injured neurons following thoracic spinal cord injuries. Advanced Cell Technology was the second such company to conduct human trials with human ES-derived retinal pigment epithelial (RPE) cells for retinal disorders. To date, Advanced Cell Technology has reported no adverse events and preliminary evidence of efficacy in age-related macular degeneration, the leading cause of blindness in an aging population. Cell Cure Neurosciences in Jerusalem is also nearing an IND filing for the use of human ES cell-derived RPE cells for the treatment of the dry form of age-related macular degeneration. The California Institute for Regenerative Medicine also reports that numerous potential INDs for human ES cell-derived products are to be expected soon in California.

Summary

Regenerative medicine, like previous revolutions in medicine such as recombinant DNA or hybridoma technology, has significant untapped potential to alleviate human suffering while simultaneously reducing health care costs by providing direct regeneration of diseased tissue as opposed to chronic ameliorative (and expensive) treatment. The regulatory pathway for advancing this science from the laboratory bench to the patient must be a bridge and not a barrier to bring the fruits of this breakthrough to people. There are concerns that the marketing of HCT/Ps in the absence of robust efficacy data may flood the market with products with little to no scientific merit or, even worse, manipulate gullible consumers with "snake oil." This is a legitimate concern, of course, but perhaps the perfect societal restraints should not become the enemy of the good. Our society will be facing enormous stress because of the challenge of degenerative disease in the baby boom generation. We suggest that the greater good of society and the advance of medicine require that the regenerative medicine community rethink an optimum system of regulatory oversight. This will require a regulatory pathway that is as innovative and revolutionary as the therapies it regulates. The progressive approval pathway provides one such structure for considering how to tailor the regulatory approval procedure for this new generation of cell-based therapeutics.

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A.I.C.: manuscript writing, final approval of manuscript; M.D.W.: manuscript writing.

Disclosure of Potential Conflicts of Interest

A.I.C. has compensated intellectual property rights with Osiris Therapeutics through the University and uncompensated stock options in Cell Bank Technologies. M.D.W. has compensated employment as chief executive officer of BioTime and subsidiaries, compensated intellectual property rights, research funding, and stock options with BioTime.

