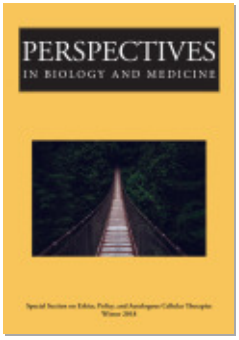
Conditional Approvals for Autologous Stem Cell–Based Interventions: *Conflicting norms and institutional legitimacy*



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conflicting norms and institutional legitimacy

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ABSTRACT Demands from patients, health-care professionals, and industry to streamline the market approval process for promising new therapies has prompted the introduction of programs that can provide more rapid access to stem cell–based products before evidence of safety and efficacy has been demonstrated in clinical trials. These products may be approved for marketing under "conditional authorizations," while uncertainty around safety and efficacy is reduced through the collection of clinical data in observational trials or registries. The rationale for conditional approval programs assumes that patients with unmet medical needs will benefit with rapid access to novel stem cell therapies. It also assumes that data gathered in actual clinical contexts

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is inherently better at reducing uncertainty than conventional clinical trial methods of demonstrating safety and efficacy. These assumptions may be overly optimistic and do not account for the broader societal burdens of prematurely releasing high-cost therapies with uncertain safety risks and benefits on to health-care markets. This essay focuses on the introduction of conditional approval programs for autologous somatic stem cell therapies and argues that these programs may conflict with, and potentially undermine, the normative commitments of regulatory agencies charged with promoting population health and protecting vulnerable groups from harm and exploitation. It concludes with suggestions of how programs designed to accelerate access to potentially helpful but experimental interventions could be reconfigured to be more equitable.

Regulators around the world are coming under pressure from patients, clinicians, and industry groups to streamline the market approval process for highly novel biomedical technologies, including stem cells and regenerative medicine products. The rationale for streamlining this process centers on the perceived failures of regulatory systems to encourage biomedical innovation and provide patients with timely access to potentially beneficial yet experimental therapies. Critics claim that the process of generating scientific evidence in phased clinical trials is too costly, time-consuming, and poorly suited for stem cell–based products that, unlike bio-pharmaceuticals, are intended to engraft into the body for long periods of time, if not permanently (Caplan and West 2014). These critics argue that the conventional pharmaceutical model is unable to adequately forecast and control for the many uncertainties of stem cell–based products, including the genetic and phenotypic profile of engraftments, which may change over time once the cells are transplanted. Such uncertainties are likely to require monitoring over the long term to fully evaluate the safety and efficacy of these products, potentially delaying access to promising new therapies.

In response to demands for more timely access, some regulators have introduced programs that can provide "conditional approvals" for sponsors to market stem cell–based products prior to completing late-stage efficacy trials. The European Medicines Agency (EMA) and Japan's Pharmaceutical Medicines and Devices Agency (PMDA) have both introduced accelerated programs for which sponsors of stem cell–based products may apply; the Japanese program is specifically for regenerative medicine products as authorized under the recently amended Pharmaceutical, Medical Devices and Other Therapeutic Products Act (PMD Act) (Azuma 2015). The US Food and Drug Administration (FDA) has since followed suit with the introduction of the new "Regenerative Medicine" designation as authorized under the 21st Century Cures Act (114–255 Pub.L.). These policies allow sponsors to commence marketing after demonstrating *probable* benefit in early phase clinical trials or with a surrogate endpoint.[1] The ap-

[1]According to the Biomarkers Definitions Working Group (2001) of the National Institutes of Health, a surrogate endpoint is a biomarker that can be "objectively measured and evaluated as an indication of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic

provals may come with conditions that additional data with clinical endpoints or in larger patient populations are submitted for full evaluation. The rationale for these schemes is to allow rapid market access for products that have demonstrated some likely benefit for patients with unmet medical needs who have limited or no effective treatment options available to them, while uncertainty around safety and efficacy is reduced from data gathered in actual clinical situations (Eichler et al. 2008).

While it is hoped that these programs will streamline the approval process for beneficial stem cell–based products, there are also concerns that premature market entry may merely promote the use of unsafe and ineffective therapies that lack robust evidence of clinical benefit (Cyranoski 2015). Such concerns are substantiated with evidence of experience with other products that have previously entered the market through an accelerated pathway. For example, problems with premature market entry have included setbacks in recruiting sufficient numbers of patients onto statistically powered trials that can demonstrate efficacy; poor correlations between the use of surrogate (instead of clinical) endpoints with primary outcomes, such as survival rates or extended quality of life; and delays in the product being withdrawn from the market when found to be inefficacious or unsafe (Aronson 2005; Darrow, Avorn, and Kesselheim 2014; Kim and Prasad 2015; Onakpoya, Heneghan, and Aronson 2015). Of particular relevance, was the premature introduction of autologous stem cell transplants with high dose chemotherapy for breast cancer patients in the 1980/90s, which delayed eventual findings that the therapy was no more effective and potentially more harmful than the standard of care (Farquhar et al. 2005). These delays incurred immeasurable opportunity costs to many thousands of patients, in addition to significant financial burdens on health insurance providers (Rettig et al. 2007). This raises critical questions around whether rapid market access to therapies that lack scientific evidence of safety and efficacy is an equitable or fair distribution of limited health-care resources.

In this essay, we scrutinize these early-access programs to argue that conditional approval schemes for highly novel stem cell–based products have the potential to undermine the moral basis and institutional norms that give legitimacy to public health regulatory agencies.[2] To ground this abstract argument, the analysis will focus on the two autologous stem cell–based products for which the respective agencies have granted conditional market authorization: Holoclar, a limbal stem cell product for the treatment of corneal burns in the European

intervention" (91). These biomarkers can be used as a surrogate for clinical endpoints, which reflect "how a patient feels, functions, or survives."

[2]We acknowledge that this analysis may also apply to other high-cost pharmaceutical and biological drug products. However, we limit our analysis to stem cells, because such programs are being established especially for these and other regenerative medicine products.

Union; and HeartSheet, a musculoskeletal stem cell product for the treatment of acute chronic heart failure in Japan. After briefly describing the programs with reference to these products, we identify important health and economic costs to show how the distribution of the benefits and burdens across the societal groups with interests in the clinical translation of stem cells is unjust.

With only two stem cell–based products approved through these accelerated programs to date, our claims are necessarily limited. It is our contention that these conditional approval programs may conflict with the normative commitments of public health and regulatory agencies to protect the public and promote good health by lowering evidentiary standards for true clinical benefit and jeopardizing patient safety without any clear benefits for the social institutions that may be burdened with these costs. While it is ethically justifiable to depart from conventional approval processes in certain circumstances of unmet medical needs, we argue that unmet medical needs should be more narrowly construed to give meaningful consideration to those patients who are worse off. Recognizing the need for innovative regulatory mechanisms for autologous cell products, we suggest ways in which these programs can be reconfigured in keeping with the moral responsibilities of public health authorities.

Accelerated Market Access for Autologous Stem Cells

As autologous cells are sourced from the same donor/recipient, they are often perceived as carrying fewer risks than other sources of stem cells, even though the safety of various sources differs with (among other concerns) their intended uses, degree of manipulation, and route of administration (Power and Rasko 2011). This perception reflects the risk-based frameworks that many regulators have adopted for cell and tissue-based products. These frameworks often have mechanisms that may exclude or exempt from regulation autologous products that are used under specific circumstances (Lysaght et al. 2017). For instance, uncultured autologous cells that are intended to replace or repair cells that have the same function may be exempted from FDA regulation under the US Public Health Services Act (1944) and under the Tissue and Cells Framework Directive (2004/23/EC). Yet, the introduction of conditional approval schemes for riskier stem cell products that are grown to unnaturally large numbers outside the body suggest that a shift in risk tolerance within public health agencies may be emerging. In this section, we provide an overview of these schemes with reference to the two autologous stem cell–based products that have been granted conditional approvals from the European EMA and the Japanese PDMA.

Conditional Approvals for Stem Cells under the EMA

The EMA is the decentralized public health agency that oversees and monitors the evaluation of medicines for sale and distribution within the single EU market. The EMA regulates stem cells as advanced therapy medicinal products (ATMP), where the safety and efficacy of ATMPs are evaluated from data collected in phased clinical trials. The European Commission approves and grants marketing authorization based on recommendations by the 'EMA's expert committee.

The EMA's conditional market approval scheme was introduced in 2006 as part of wider efforts to improve access for patients with unmet medical needs to novel therapeutics within the EU. From 2006 to 2016, the EMA granted 30 conditional approvals, with 11 of those having been converted into full market authorizations (EMA 2016). According to the EMA's report, almost half of those products were designated as "orphan medicines," treatments for rare, seriously debilitating, or life-threatening conditions affecting less than five in 10,000 individuals in the EU. At the point of conditional authorization, more than half were of the products evaluated with evidence from at least one phase III trial. Under the scheme, sponsors may be subject to specific obligations, which are reviewed annually, and the conditional approvals are renewable each year following review. While timeframes may be set in meeting requirements for conditional approval, extensions may be granted.

The first conditional authorization for an ATMP was granted in December 2014 as part of the EMA's two-year pilot for an accelerated program called the "Adaptive Pathways" (EMA 2014b), which was introduced in response to calls for faster access to innovative biomedicines (Eichler et al. 2014). During the pilot program, the EMA selected the limbal stem cell product, Holoclar (Lee and Lysaght 2017). This product consists of cultured autologous human corneal epithelium containing limbal stem cells that are surgically transplanted into patients for the treatment of limbal stem cell deficiency resulting from ocular burns, a rare injury affecting an estimated patient population of just 1,000 people in the EU. Designated an orphan medicine, Holoclar was approved on the basis of two retrospective studies of outcomes data from n = 135 (out of 219) patients who had received the transplant between 1998 and 2007 (Milazzo et al. 2016). Primary endpoints measured were stable corneal epithelium, and secondary endpoints were the degree of pain and burns 12 months after the operation. The product is approved on the conditions that the sponsor submit the results of a multinational, prospective, open-label, uncontrolled study to assess the efficacy and safety of the product by 2020. Success with Holoclar will likely create a clear pathway for granting conditional approvals to other stem cell–based products.

Conditional Approvals for Stem Cells under the PMDA

The PMDA is the public health agency established under the Ministry of Health, Labour and Welfare (MHLW) to evaluate and monitor medicines entering the Japanese market. Until 2015, stem cells were not regulated by the PMDA unless they could be classified as drugs or devices (Azuma 2015). However, following recent reforms to the Pharmaceutical, Medical Devices and Other Therapeutic Products Act (PMD Act), the regulator is now authorized to evaluate the safety and efficacy of stem cells and other regenerative medicine products for market distribution. Upon evaluation, the PMDA submits an opinion to the MHLW, which ultimately grants market approval or makes further recommendations for review.

As mentioned previously, Japan's conditional approval program was implemented as part of reformations to the PMD Act, and it is specifically intended for regenerative medicine products, including stem cells. Like the EMA program, it is intended to address unmet medical needs or serious life-threatening illnesses (Sato, Arakawa, and Isobe 2016). The Act provides sponsors with a conditional and time-limited approval to market their products once safety and *probable benefit* has been demonstrated in exploratory trials with a surrogate endpoint (Konomi et al. 2015). This provision may allow the regulator to accept evidence from as early as a phase I/II study before conditionally approving the product. Sponsors will then have a maximum of seven years to submit data that further evaluates efficacy.

To date, the MHLW has granted conditional authorization for one product: HeartSheet, an autologous skeletal myoblast sheet product for the treatment of severe chronic heart failure (CHF). As a disease affecting 23 million people worldwide, and close to a million in Japan (Konishi et al. 2016), CHF is not an orphan disease, but it has limited treatment options. HeartSheet was conditionally approved for CHF in 2015 after a phase I/II study with just seven patients (Konishi et al. 2016). This study measured surrogate endpoints with computed tomography and ultrasonography, but also measured changes in left ventricular ejection fraction (LVEF) with cardiac scintigraphy as primary endpoints (Sawa et al. 2015). While the LVEF showed no improvements at 26 weeks, five out of the seven patients did not worsen, which the regulator accepted as a clinical benefit. The license conditions require the sponsor to compare the survival rates of n = 60 patients with an external concurrent cohort of 120 patients receiving standard treatments over five years in an observational post-marketing study.

Conditional Approval for Stem Cells: An Erosion of Institutional Norms?

While both Holoclar and Heartsheet are intended to address unmet medical needs, it is unclear from their respective conditional approvals how much benefit

patients will actually gain from the products or how much the treatments will cost, either directly out of pocket or within a health-care system. These ethical considerations are important for regulators, because they reflect moral values that underpin the normative mission of public health agencies to protect and promote good health in processes that are fair and minimize social injustices (Kass 2001). Public health is concerned with protecting and promoting the health of populations (Faden and Shebaya 2016); given the direct distributive role that public health plays in shaping population-level health outcomes (Gostin and Powers 2006), it can be further argued that these obligations extend to public health agencies, where values such as fairness, justice, and beneficence support and give expression to their institutional legitimacy and moral authority.

Two broad questions thus guide the ensuing analysis: whether conditional approval schemes for autologous stem cell products promote the social and moral values of fairness, and whether institutionalizing regulatory schemes that lower the evidentiary standards for clinical beneficence align with the normative commitments of public health to protect and promote good health. To address these questions, we now turn to the broader health and economic implications of the conditional approval programs by evaluating who stands to benefit from these programs, and at what cost.

Who Benefits at What Cost?

Our analysis focuses on the societal group at the center of moral justifications that are frequently made for accelerating the market authorization process for stem cell therapies: patients with unmet medical needs. This group may consist of patients suffering rare diseases or orphan conditions that affect so few people that developers are deterred from investing in the long-term clinical studies needed to gain market authorization through the conventional approval pathway. This group may also include large cohorts of patients suffering serious or life-threatening conditions. In both cases, the unmet need arises primarily from having no or limited effective treatment options available; where treatments do exist, the therapeutic candidate must be able to demonstrate superiority in benefit or harm minimization (EMA 2016). The opportunity for providing this group with much faster access to promising new therapies meant to offset ethical concerns about the uncertain safety risks and the unclear benefits (Eichler et al. 2008). But is it ethically justifiable to burden patients who, by definition, lack options when clear evidence of clinical benefit is absent?

For Holoclar, evidence of clinical benefit is indicated in two retrospective studies of patient outcomes over almost 20 years in the context of clinical care.[3] The

[3]The product only came under EMA regulation following the introduction of the AMPT Regulations in 2007, at which point the developers had to comply with good manufacturing practice requirements and submit retrospective clinical data in compliance with ICH-E6 and E3 guidelines (Milazzo et al. 2016).

small sample size reflects the low prevalence of ocular burns in the EU, and while open-label retrospective studies are ordinarily considered as weak evidence, clinical endpoints included evidence of both tissue regeneration and reduced pain/improved vision. Thus, it is reasonable to expect that patients enrolled in the follow-up prospective study will experience benefit, and those benefits are likely to be significant for patients with moderate to severe limbal stem cell deficiency who are otherwise experiencing debilitating pain and discomfort from burns and photophobia (light sensitivity).

The evidence of clinical benefit from Heartsheet, on the other hand, is much weaker, with an open-label study on a very small sample of just seven patients from a potential population of close to a million with CHF. According to the developer's dossier, patients selected for the trial were categorized with a New York Heart Association Heart Functional Classification of III–IV, were nonresponsive to standard medications, and were in a worsening condition. As the condition of the surviving patients in that trial did not worsen at 26 weeks (or improve), clinical benefit may be indicated and would likely justify moving the product into a phase II trial with a larger cohort. However, without any comparator controls, or evidence demonstrating the alleviation of symptoms, it is difficult to draw conclusions that would support a marketing authorization for this product at this stage. The reported effects could be explained by placebo, and it is unclear what, if any, effects the myoblast sheets are having on the regeneration or repair of heart tissue. Thus, the evidence cannot support any marketing claims of heart repair and is unlikely to support any reasonable expectation of substantial clinical benefit for patients receiving the product in the five-year conditional period.

Given these benefits—or lack thereof—what burdens do these products expose patients to? Many types of costs may burden patients who access novel stem cell therapies. The most salient for public health are physical and financial harms, although there may be other important costs to individuals. For example, opportunity costs may arise when an individual patient forgoes a conventional treatment for a novel therapy or becomes ineligible to enroll in future clinical trials with other promising interventions due to the presence of engrafted cells (Hyun 2013). Emotional and psychological harms can also arise when vulnerable patients who have limited options and are desperate for treatment consent to an unproven intervention and experience little to no benefits (Petersen et al. 2017). However, to focus our analysis on to the issues that matter most to public health agencies approving autologous stem cell–based therapies, we consider the burdens of irreversible physical harms from adverse events, and the financial costs for patients and for health-care systems.

Irreversible Physical Harm

Stem cells are unlike biopharmaceutical products or biologics, in that they are intended for permanent or long-term engraftment: if there are adverse side

effects, they cannot be metabolized from the body, and surgical removal may be impractical or incur greater risk. Both Holoclar and HeartSheet are sheets of autologous cultured tissues that are designed to engraft and regenerate damaged tissues. After engraftment, they cannot be easily removed without risking further injury. For patients receiving Holoclar, removal of the engrafted product might, at worst, result in the loss of an eye that was already non-functional from extensive burns. However, open chest surgery to remove an engrafted HeartSheet from an already failing vital organ is likely to result in death. There are also risks that the product might cause arrhythmia or complete heart failure (Terajima et al. 2014), whereas the potential harms from Holoclar include corneal damage and inflammation, painful but manageable conditions (EMA 2014a).

Japanese patients suffering an adverse event from HeartSheet, or any other approved drug, can apply for compensation through the Adverse Reaction Relief Fund System. This fund is supported with government subsidies and contributions from marketing authorization holders based on annual sales (Azuma 2015). Patients can apply for financial assistance if hospitalized from an injury, for a disability pension in the event of serious impairment, and, in the case of death, for compensation for the bereaved family and assistance with funeral costs (Miyazaki 2010). This system redistributes some of the financial burdens of an adverse event away from patients and back on to manufacturers, providing them with an incentive for establishing a well-understood safety profile prior to commercialization. However, government subsidization also taxes public resources, which means that regulators have a special obligation to ensure these funds are used fairly and benefit those who need it the most. Prematurely authorizing highly novel therapeutics without good evidence of safety and efficacy might counter that goal.

Financial Costs

Therapies based on living cells are inherently expensive, especially autologous stem cells, which are derived for each individual patient and cannot be standardized like 'off-the-shelf' products from donor cells or drugs. These products are labor-intensive, requiring highly trained technical personnel and specialized medical professionals to administer, and in most industrialized countries, they must be processed under sterile conditions in dedicated facilities according to good manufacturing practices (GMP). If the GMP facility is not onsite, then additional costs are incurred in storage and shipment.

In this respect, Holoclar and Heartsheet are no exception. Shortly after being granted authorization, HeartSheet was listed on the National Health Insurance (NHI) with a price of up to US$147,000, which is reimbursable throughout the conditional period (Okada, Miyata, and Sawa 2017). While Japan's social health insurance operates under a co-payment system, those costs are capped to maximum amounts under the High Cost Medical Care Scheme according to income and age (IBM Japan Health Insurance Association 2016). One commentator esti-

mates that the cost of HeartSheet for a middle-income patient under 70 years old would be limited to approximately US$1900 a month (Sato, Arakawa, and Isabe 2016), meaning that the NHI will bear the primary costs of stem cell products approved under the conditional program.

The manufacturers of Holoclar received their first price listing in July 2017, two and half years post approval. The National Institute for Health and Care Excellence (NICE) in the United Kingdom has recommended Holoclar for routine use within National Health System (NHS) for patients with moderate to severe limbal stem cell deficiency. NICE (2017) recommended that Holoclar should only be used to treat one eye, and in patients who have either already had a conjunctival limbal autograft, or where there is not enough tissue in the healthy eye for this standard of care approach or it is contra-indicated. This recommendation was based on calculations of quality-adjusted years (QALY) for cost-effectiveness, even though the evaluating committee at NICE concluded that Holoclar was *not* a cost-effective use of NHS resources, except when compared with the best supportive care (in other words, lubrication, eye drops, and contact lenses). To offset the burdens on the NHS, the manufacturer of Holoclar is providing a discount to its £80,000 per treatment cost under the Patient Access Scheme (PAS), although the discounted price is not publically available as commercially sensitive information. Thus, the full cost of the product to the NHS is unclear.

Similar assessments of cost-effectiveness for HeartSheet are not available because, according to Okada, Miyata, and Sawa (2017), health technology assessment is relatively new in Japan and does not (yet) include indices for key clinical outcomes, such as QALY. However, given the lack of evidence that demonstrates significant benefits for patients, HeartSheet is probably not a cost-effective use of Japan's NHI resources, either.

What has likely influenced the decision to support these products with public health funding is recognition that novel cell-based therapies will otherwise be out of reach for many years to most patients suffering these conditions. Yet novelty or innovation is not sufficient justification alone for expending limited public resources where the evidence based is weak and without reasonable expectation that the therapy can confer very substantial health gains. Given the low prevalence of moderate to severe corneal burns, the potential harms and financial burdens of Holoclar are spread across a very small number of patients who can be reasonably expected to benefit immensely from a successful engraftment. As mentioned previously, these patients not only suffer visual impairment but chronic pain and light sensitivity from the burns. In contrast, for Heartsheet, this kind of distribution is less sustainable, with potentially far more patients being exposed to high risks of harm without such marked gains. The costs to Japan's health-care system, already strained with an aging population and shrinking workforce (Reich and Shibuya 2015), could be significant, and thus might not be a just use of public resources.

From the analysis of these two products, it is unclear that many patients with unmet medical needs are set to benefit from the conditional approval of autologous stem cell therapies. With Holoclar, a few patients may benefit a lot; with HeartSheet, more patients may benefit very little, if at all. Neither has been demonstrated as a cost-effective use of public health-care resources, except in the use of Holoclar against standard supportive care. Thus, the redistribution of burdens from individual patients and the commercial sponsors, who are set to benefit with reduced economic risks that are normally associated with product development, to public health systems may be difficult to justify, at least in the case of HeartSheet. The question we turn to now is whether these outcomes align with or undermine the institutional legitimacy of public health laws and agencies.

Social Justice and Institutional Legitimacy

Government agencies and health-care policies, laws, and regulations play powerful roles in the distribution of health and economics benefits and burdens across society. How these benefits and burdens are distributed affects the lives of individuals and populations in profound and fundamental ways. Limited access to health care, for instance, affects an individual's ability to participate meaningfully in the political, economic, and social life (Daniels and ACLS 1985). As conditional approval schemes become mainstreamed into national regulatory frameworks, they are likely to impact population health, and to that extent, the range of opportunities available to individual patients in the present, as well as those in the future. In considering the alignment of these programs with the normative goals of public health agencies, we examine the wider sociopolitical implications of institutionalizing regulations that lower the evidentiary standards for safety and clinical benefit of medical interventions.

In general, governments have a duty to protect the public and vulnerable populations from harm (Hutt 1980). In the EU, the EMA (2017) functions as the gatekeeper to ensure all drugs that are available on the market have a safety profile that is proportional to the expected benefits. Similarly, in Japan the PMDA (2004) has an "obligation to protect the public health by assuring safety, efficacy and quality of pharmaceuticals and medical devices"; these duties now extend to regenerative medicine products. The duty to protect gives public health agencies the moral license to infringe on individual freedoms in determining what products are available on the marketplace. Public health agencies express and demonstrate their normative purpose by preventing and deterring sub-par and unsafe therapies from entering health-care systems.

Accordingly, public health agencies are responsible for ensuring that therapeutic and medicinal products meet statutory standards of safety *and* efficacy. Indeed, the World Health Organization (2003) identifies the assessment of safety, efficacy, and quality of medicines as a key regulatory function of public health

agencies. Efficacy relates to intended benefits, which are needed to justify the expected harms and associated risks of clinical interventions. Governments owe to their constituents a duty to protect them against unsafe, ineffective medicines against which no single individuals or groups of individuals are capable of safeguarding themselves. Likewise, patients rely on public health agencies to regulate medicines available on the market because of the scientific expertise required to oversee their distribution and production. Insofar as ensuring medical products available on the marketplace are safe and of good quality requires government actions, public health agencies' legitimacy relies upon their ability to regulate the marketplace in meeting these societal expectations.

Furthermore, as patients generally lack specialized knowledge about when and which therapeutics to use, at what dosage, and how to weight potential benefits against risks, they rely on professional advice from their doctors. In turn, medical professionals rely on labelling information about appropriate indications, contra-indications, dosage, administration, side effects, and risks, as supported with scientific evidence that regulators evaluate for the marketing approval. If the standards of evidence required for these evaluations are lowered under an accelerated approval program, then medical professionals are less able to meet their moral obligations of providing clinical care that is evidence-based and of acting in ways that benefit their patients. Medical doctors self-regulate under professional norms and standards that are violated when practicing without sound evidence of patient safety and clinical beneficence (Munsie and Hyun 2014). These violations could undermine public trust in medicine and erode the epistemic and moral authority of the medical profession, which may be exacerbated by the institutionalization of programs that lower the standard of evidence for therapeutic products entering the marketplace.

With only two products to assess, it is difficult to evaluate how well the particular schemes of the EMA and PMDA align with the normative goals of public health and medicine. In any case, the introduction of these programs and their impetus on fast-tracking what is ordinarily a time-consuming and costly process reflects the economic and political imperatives that are driving global competition to innovate and deliver new biomedical interventions. These imperatives are underpinned by an ideology that prioritizes free-market enterprise and individual choices to access innovative therapies over the need for scientific evidence that demonstrates the safety and efficacy (Bipartisan Policy Center 2015). These priorities are at odds with the institutional norms of public health agencies, which must prioritize wider societal interests in delivering safe and effective therapeutic products to future patients over the present demands of individual patients and industries to access open markets for expensive and risky experimental therapies. As pressure mounts on regulators to authorize highly novel therapeutic products prematurely, the institutional legitimacy and moral authority of public health agencies is weakened.

The weakening of public health institutions ought to be of concern, as these agencies not only enable equitable market access to safe and efficacious healthcare products, but they also promote good science and the societal benefits that come from it. Society benefits from carefully designed research, and enabling premature market access to novel therapies based on weak evidence may negatively disrupt the production and value of scientific knowledge. Any major adverse event arising from the early market approval of a novel stem cell therapy has the potential to undermine public trust and negatively impact on the fields of stem cell science and regenerative medicine as it emerges (Lysaght et al. 2017). This outcome benefits no one.

Perhaps most importantly from a justice perspective, the needs of all persons, including those who are medically worst off, must be taken into account. Hence, in certain circumstances it may be ethically justifiable to depart from conventional approval processes to provide interventions to patients who suffer from rare, seriously debilitating, or life-threatening diseases. Yet the definition of "unmet medical need" may be too broadly construed for this purpose. While the PMDA does not specify criteria that products should meet (Jokura, Yano, and Yamato 2017), the EMA defines "unmet medical need" as a "condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorized in the Community or, even if such a method exists, in relation to which the medicinal product concerned will be be of major therapeutic advantage to those affected" (EMA 2016, 4). However, what constitutes an unsatisfactory method or major therapeutic advantage could apply to much larger patient populations than intended for this exceptional category.

If public health agencies are to treat fairly those who are medically worst off and to maximize health benefits from available resources, it may be necessary to construe "unmet medical need" more narrowly. A narrow definition might also be necessary in practice, because depending on how diagnostic criteria are defined, unmet medical needs can exist as a matter of degree (Smith and Brindely 2017). One way to counter an expansive reading of the term might be to limit the criteria to rare, debilitating disease conditions that are suffered by a small, defined patient group—at least until uncertainties around classification, characterization, manufacturing, and quality assurance processes for autologous stem cells can be reduced (although not necessarily eliminated) and their applications become more cost-effective (Hourd et al. 2014).

There are other reasons for supporting a narrow interpretation for addressing unmet medical needs with autologous stem cell products. First, patient recruitment into clinical trials for rare diseases is inherently difficult, which limits patient access to medical products. Second, from a regulatory perspective, narrowing the definition would deter sponsors from pursuing conditional approvals simply because data sets are not sufficiently robust for the conventional pathways. Indeed, some scholars are of the view that Japan has applied the PMDA accelerated

program to prioritize one therapeutic approach over others, instead of focusing on meeting the medical needs of patients who suffer from rare, seriously debilitating, or life-threatening diseases (Smith and Brindely 2017). With a narrow construction of unmet medical need, accelerated programs can better align with the normative functions of public health agencies and maintain their moral and institutional legitimacy.

Conclusion

The introduction of conditional approval schemes for high-cost autologous stem cell–based products does not reconcile with norms and values that legitimize the moral and social obligations of public health agencies. Health care is a key socially controllable determinant affecting population health and its distribution, and a societal commitment to social justice is manifested through social provisions that guarantee fair equality of opportunity. Appeals to fairness and social justice highlight the nuanced moral demands entrusted in public health agencies. If we take all lives as having equal value seriously, then there is a strong moral justification for fair allocations of common advantages and the sharing of common burdens.

This essay, therefore, can be read as a defense of the public health agencies that are responsible for regulating the manufacturing and marketing of autologous stem cell products. We acknowledge that greater regulatory flexibility is needed, given the difficulty in standardizing, reproducing, and testing stem cell–based products in large-scale efficacy trials, especially when invasive surgical procedures are required for transplantation. However, the solution is not simply to leave it to market demands to determine if such products are safe and effective. While in future there may be scope to conditionally approve autologous therapies—and indeed other regenerative medicine products—the ongoing uncertainty surrounding the mechanisms, safety and functionality of stem cells is going to require the careful evaluation and assessment that public health agencies can provide.

We have suggested that a narrowly tailored program for approving stem cell–based products would better align with the central mission of public health agencies while accommodating the specific demands from patients with unmet medical needs. Currently, any therapeutic candidate that is potentially better than an existing product can qualify as meeting an unmet medical need, meaning that *all* patients potentially have such needs, irrespective of the availability of therapeutic options. This configuration appears unfair to patients suffering rare or life-threatening conditions for which little or no effective options are available. The impacts of programs that qualify as therapeutic products for such wide-ranging conditions potentially create greater burdens on health care systems and professional standards without corresponding gains. Preserving sustainable health-care systems for patients in the present, as well as those in the future, is a

societal and moral obligation that ought to underpin the normative commitments of public health agencies responsible for promoting population health.

References

Aronson, J. K. 2005. "Biomarkers and Surrogate Endpoints." *Br J Clin Pharmacol* 59 (5): 491–94. DOI: 10.1111/j.1365-2125.2005.02435.x.

Azuma, K. 2015. "Regulatory Landscape of Regenerative Medicine in Japan." *Curr Stem Cell Rep* 1 (2): 118–28. DOI: 10.1007/s40778-015-0012-6.

Biomarkers Definitions Working Group. 2001. "Biomarkers and Surrogate Endpoints: Preferred Definitions and Conceptual Framework." *Clin Pharmacol Ther* 69 (3): 89–95. DOI: 10.1067/mcp.2001.113989.

Bipartisan Policy Center. 2015. *Advancing Regenerative Cellular Therapy: Medical Innovation for Healthier Americans*. Washington, DC: Bipartisan Policy Center. http://bipartisanpolicy.org/wp-content/uploads/2015/12/BPC-Advancing-Regenerative-Cellular-Therapies.pdf.

Caplan, A. I., and M. D. West. 2014. "Progressive Approval: A Proposal for a New Regulatory Pathway for Regenerative Medicine." *Stem Cells Transl Med* 3 (5): 560–63. DOI: 10.5966/sctm.2013-0180.

Cyranoski, D. 2015. "Stem the Tide." *Nature* 528: 163–64.

Daniels, N., and American Council of Learned Societies (ACLS). 1985. *Just Health Care*. New York: Cambridge University Press.

Darrow, J. J., J. Avorn, and A. S. Kesselheim. 2014. "New FDA Breakthrough-Drug Category: Implications for Patients." *N Engl J Med* 370 (13): 1252–58. DOI: 10.1056/NEJMhle1311493.

Eichler, H.-G., et al. 2008. "Balancing Early Market Access to New Drugs with the Need for Benefit/Risk Data: A Mounting Dilemma." *Nat Rev Drug Discov* 7 (10): 818–26.

Eichler, H.-G., et al. 2015. "From Adaptive Licensing to Adaptive Pathways: Delivering a Flexible Life-Span Approach to Bring New Drugs to Patients." *Clin Pharmacol Thera* 97 (3): 234–46.

European Medicines Agency (EMA). 2014a. *Holoclar Summary of Product Characteristics*. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002450/WC500183404.pdf.

European Medicines Agency (EMA). 2014b. "Status of the Adaptive Pathways Pilot Project." http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/12/news_detail_002244.jsp&mid=WC0b01ac058004d5c1.

European Medicines Agency (EMA). 2016. *Conditional Marketing Authorisation: Report on Ten Years of Experience at the European Medicines Agency*. London: EMA. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2017/01/WC500219991.pdf.

European Medicines Agency (EMA). 2017. About Us. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/08/WC500211862.pdf.

Faden, R., and S. Shebaya. 2016. "Public Health Ethics." In *The Stanford Encyclopedia of Philosophy,* ed. E. N. Zalta. https://plato.stanford.edu/.

Farquhar, C., et al. 2005. "High Dose Chemotherapy and Autologous Bone Marrow or Stem Cell Transplantation versus Conventional Chemotherapy for Women with Metastatic Breast Cancer." *Cochrane Datab Syst Rev* 3. DOI: 10.1002/14651858.CD003142.pub2.

Gostin, L. O., and M. Powers. 2006. "What Does Social Justice Require for the Public's Health? Public Health Ethics and Policy Imperatives." *Health Aff (Millwood)* 25 (4): 1053–60. DOI: 10.1377/hlthaff.25.4.1053.

Hourd, P., et al. 2014. "Manufacturing Models Permitting Roll Out/Scale Out of Clinically Led Autologous Cell Therapies: Regulatory and Scientific Challenges for Comparability." *Cytotherapy* 16 (8): 1033–47. DOI: 10.1016/j.jcyt.2014.03.005.

Hutt, P. B. 1980. "Five Moral Imperatives of Government Regulation." *Hastings Cent Rep* 10 (1): 29–31. DOI: 10.2307/3560502.

Hyun, I. 2013. *Bioethics and the Future of Stem Cell Research*. London: Cambridge University Press.

IBM Japan Health Insurance Association. 2016. "When You Incur High Medical Care Costs." http://www.ibmjapankenpo.jp/eng/member/benefit/expensive_a.html.

Isasi, R., V. Rahimzadeh, and K. Charlebois. 2016. "Uncertainty and Innovation: Understanding the Role of Cell-Based Manufacturing Facilities in Shaping Regulatory and Commercialization Environments." *Appl Transl Genomics* 11: 27–39. DOI: 10.1016/j.atg.2016.11.001.

Jokura, Y., K. Yano, and M. Yamato. 2017. "Comparison of the New Japanese Legislation for Expedited Approval of Regenerative Medicine Products with the Existing Systems in the USA and European Union." *J Tissue Eng Regen Med*. DOI: 10.1002/term.2428.

Kass, N. E. 2001. "An Ethics Framework for Public Health." *Am J Public Health* 91 (11): 1776–82.

Kim, C., and V. Prasad. 2015. "Cancer Drugs Approved on the Basis of a Surrogate End Point and Subsequent Overall Survival: An Analysis of 5 Years of US Food and Drug Administration Approvals." *JAMA Intern Med* 175 (12): 1992–94. DOI: 10.1001/jamainternmed.2015.5868.

Konishi, M., et al. 2016. "Heart Failure Epidemiology and Novel Treatments in Japan: Facts and Numbers." *Esc Heart Failure* 3 (3): 145–51. DOI: 10.1002/ehf2.12103.

Konomi, K., et al. 2015. "New Japanese Initiatives on Stem Cell Therapies." *Cell Stem Cell* 16 (4): 350–52. DOI: 10.1016/j.stem.2015.03.012.

Lee, T.-L., and T. Lysaght. 2017. "Adaptive Pathways Regulations for Stem Cells: Accelerating Access to Medicine or Deregulating Access to Markets?" *SCRIPTed* 14 (1): 81–99.

Lysaght, T., et al. 2017. "Ethical and Regulatory Challenges with Autologous Adult Stem Cells: A Comparative Review of International Regulations." *J Bioethic Inq* 14 (2): 261–73. DOI: 10.1016/j.stem.2013.11.013.

Milazzo, G., et al. 2016. "Holoclar: First of Its Kind in More Ways Than One." *Cells Gene Ther Insights* 2 (2): 183–97.

Miyazaki, S. 2010. *Relief Service for Adverse Health Effects in Japan*. www.pmda.go.jp/files/000163897.pdf.

Munsie, M., and I. Hyun. 2014. "A Question of Ethics: Selling Autologous Stem Cell Therapies Flaunts Professional Standards." *Stem Cell Res* 13 (3 part B): 647–53. DOI: 10.1016/j.scr.2014.04.014.

National Institutes for Health and Care Excellence (NICE). 2017. *Final Appraisal Determination: Holoclar for Treating Limbal Stem Cell Deficiency After Eye Burns*. www.nice.org.uk/guidance/gid-ta10044/documents/final-appraisal-determination-document.

Okada, K., T. Miyata, and Y. Sawa. 2017. "Insurance Systems and Reimbursement Concerning Research and Development of Regenerative Medicine in Japan." *Regen Med* 12 (2): 179–86. DOI: 10.2217/rme-2016-0124.

Onakpoya, I. J., C. J. Heneghan, and J. K. Aronson. 2015. "Delays in the Post-Marketing Withdrawal of Drugs to Which Deaths Have Been Attributed: A Systematic Investigation and Analysis." *BMC Med* 13 (1): 26. DOI: 10.1186/s12916-014-0262-7.

Petersen, A., et al. 2017. *Stem Cell Tourism and the Political Economy of Hope*. London: Palgrave Macmillan.

Pharmaceutical and Medical Devices Agency (PMDA). 2004. Outline of PMDA. https://www.pmda.go.jp/english/about-pmda/outline/0005.html.

Power, C., and J. E Rasko. 2011. "Promises and Challenges of Stem Cell Research for Regenerative Medicine." *Ann Intern Med* 155 (10): 706–13. DOI: 10.1059/0003-4819-155-10-201111150-00010.

Reich, M. R., and K. Shibuya. 2015. "The Future of Japan's Health System: Sustaining Good Health with Equity at Low Cost." *N Engl J Med* 373 (19): 1793–97. DOI: 10.1056/NEJMp1410676.

Rettig, R. A., et al. *False Hope: Bone Marrow Transplantation for Breast Cancer*. New York: Oxford University Press.

Sato, D., Y. Arakawa, and S. Isobe. 2016. "Response to Nature's Editorial Regarding the Japanese legal System for Regenerative Medicines." *Regen Ther* 4: 103–4. DOI: 10.1016/j.reth.2016.04.003.

Sawa, Y., et al. 2015. "Safety and Efficacy of Autologous Skeletal Myoblast Sheets (TCD-51073) for the Treatment of Severe Chronic Heart Failure Due to Ischemic Heart Disease." *Circ J* 79 (5): 991–99. DOI: 10.1253/circj.CJ-15-0243.

Smith, J. A., and D. A. Brindley. 2017. "Conditional Approval Pathways: The 'Special' Case of Global Regenerative Medicine Regulation." *Rejuvenation Res* 20 (1): 1–3.

Terajima, Y., et al. 2014. "Autologous Skeletal Myoblast Sheet Therapy for Porcine Myocardial Infarction Without Increasing Risk of Arrhythmia." *Cell Med* 6 (3): 99–109. DOI: 10.3727/215517913X672254.

World Health Organization (WHO). 2003. *Effective Medicines Regulation: Ensuring Safety, Efficacy and Quality*. Geneva: WHO. http://apps.who.int/medicinedocs/pdf/s4921e/s4921e.pdf.