



## Commentary

## Compassionate use and hospital exemption for regenerative medicine: Something wrong to apply the program for patients in a real world

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## ABSTRACT

“Compassionate use” or “Hospital exemption” provides an important pathway for patients with life-threatening conditions to gain access to unproved human cells and tissue products. In a real world, any practitioners may not comply with relevant system. Such regulation should establish an international registry of clinical practices of stem cell therapy as well as provide education for patients to prevent deception by the spread of misinformation by testimonials on websites.

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We read the World Report titled “The dangers of unregulated stem-cell marketing” by Dara Mohammadi [1] with great interest. The article mentions that the United Kingdom (UK) and Europe have the Medicines and Healthcare Products Regulatory Agency (MHRA) and European Medicines Agency (EMA), respectively, that regulate “Compassionate exception” uses of cell therapy treatments for patients in need [1].

However, in the European Union (EU) the “Compassionate use programs” are only for patients that have life-threatening or severely debilitating diseases which cannot be treated satisfactorily with any currently authorized medicine [2]. The medicine must be undergoing clinical trials or have entered the marketing authorization application process [2]. Furthermore, the advanced therapy medicinal product (ATMP) comprising a somatic cell therapy medicinal product, a tissue engineered product, and a gene therapy medicinal product in the EU also has the centralized marketing authorization application process among the EU members' states [3]. As exception of the centralized marketing authorization application process under so-called ATMP

regulation, Regulation (EC) No 1394/2007, the “Hospital exemption” under the article 28 of ATMP regulation allows to member states that enables to permit the use of ATMPs in their territories without the requirement for marketing authorization [4]. The article applies only to custom-made ATMPs used in a hospital setting for a specific patient in situations of high unmet medical need and where no authorized products are available [4]. Such products are produced under the responsibility of a physician and are only to be used within the member state where it is produced [4]. In addition, a competent authority must authorize “Hospital exemption” for ATMPs and they must comply with the same national requirements concerning quality, traceability and pharmacovigilance that apply to authorized medicinal products [4].

Then, in the United States (US) the “Compassionate exemption” or “Special exception” is for patients who do not meet the eligibility criteria for a clinical trial of an investigational drug available for cancer treatment according to access investigational drugs of National Cancer Institute (NCI) at the National Institutes of Health (NIH) [5]. Sometimes called “Compassionate use”, mostly “Expand access” is the use outside of clinical trial of investigational drugs, biologics, and medical devices [6]. The “Compassionate use” provides an important pathway for patients with life-threatening conditions to gain access to unproved investigational drugs, medical devices, and biologics including human cells and tissue

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products [7]. Under the Federal Food, Drug, and Cosmetic Act (FD&C Act), a patient may seek “Individual patient expanded access” to investigational products for the diagnosis, monitoring, or treatment of a serious disease or condition [6]. Physician may submit a protocol intended to provide widespread access to an investigational product for multiple patients under a treatment Investigational New Drug Application (IND) or treatment Investigational Device Exemption (IDE) [6,7].

In Japan, as of 2015 there was such “Compassionate use” or “Expanded access” as the US but unapproved products were used under a physician's discretion in compliant with Japan Medical Practitioner's Act or Advanced Medical Care [7]. As this moment, however, the “Compassionate use” or “Expanded access” applies for investigational drugs, medical devices, or regenerative medicine products when the patients who could not meet the eligible criteria need during a clinical trial or after completing the clinical trial prior to approval [8].

Small and Medium Size Enterprise has the option not to participate in such programs. Participation in such programs can be prohibitively expensive for small biotech companies and potentially pose challenges in getting experimental products approved since this access occurs outside of the scrutiny of a clinical trial but can still be subject to scrutiny by regulatory agencies.

In Japan, a new law, “The Act on the Safety of Regenerative Medicine”, came into effect in 2014 to regulate medical professionals' practices and clinical studies related to regenerative medicine [9]. Similar to the ethical and scientific board application approvals usually needed in the UK and Europe for patients [10] that might qualify for “Compassionate exception” cell therapy treatments, all protocols under this new Act in Japan need pre-approval by specific ethical and scientific committees to demonstrate that appropriate accommodations are made to mitigate the presumed risks [9]. The regulation of this new legislation appears to have teeth in 2017, 11 clinics were inspected by the Japanese Ministry of Health, Labor and Welfare (MHLW) and six people were arrested for violating this new law by injecting patients with umbilical cord blood for aesthetic and anti-aging purposes without appropriate approval [11]. Thus, although, as the article acknowledges, establishing an international standard to ensure and enforce safe and effective regulation of cell therapies, the recent statement released by the Food and Drug Administration (FDA) on future regulatory changes to come [12] and the crackdowns on rouge clinics [12] and practices around the world [13–15] that have been found to be peddling unsafe cell therapies indicate that there is an international interest in regulating cell therapies. Such regulation should establish an international registry of clinical practices of stem cell therapy as well as provide education for patients to prevent deception by the spread of misinformation by testimonials on websites. Such provisions would protect the integrity of stem cell therapy research and prevent the unscrupulous few from tarnishing the promise of the nascent field.

## Contributions

Dr. Yano drafted the manuscript with references; Dr. Yamato planned and organized this study as a corresponding author.

## Competing interests

Dr. Yano is also an employee of Medtronic Japan Co., Ltd., and Dr. Yamato is a shareholder of CellSeed Inc.

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