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REVIEW

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Challenges and opportunities in the compassionate use of out-of-specification products in autologous regenerative medicine

Masao Sasai[1,2†], Yayoi Kitawaki[3,4†], Akihiro Umezawa[2,5], Yoshinori Oie[2,6], Takahiro Kamiya[2,7], Takuji Kawamura[2,8], Yoji Sato[2,9], Satoshi Hosoya[2,5], Hiroyuki Sugawara[4,10], Kazuto Yamada[4,11], Hiroshi Izumoto[4,12], Yoshiyuki Mae[4,12], Tohru Kuroda[4] and Kiyoshi Okada[2,13*]

Abstract

Background In recent years, therapeutic preparations using patient-derived tissues have emerged as commercially approved regenerative medicine products for expanding treatment possibilities for patients with no other treatment options. Autologous cell-processed products, derived from the tissue of the patient, typically exhibit variability in raw material quality, resulting in the generation of out-of-specification (OOS) products.

Main body The compassionate use of OOS products is also practiced by the Food and Drug Administration and European Medicines Agency; differences among the three regulatory authorities were investigated to identify challenges in Japan. For conditions with no alternative treatments and severe time constraints, OOS products are sometimes used under compassionate grounds, particularly in Japan, where they are administered within the framework of clinical trials. This approach, although ethical, imposes significant operational and administrative burdens on medical institutions and marketing authorisation holders, raising concerns about sustainability. We considered the rationalisation of the current system and reached the conclusion that it would not contribute to load reduction and sustainability; thus, we devised a new framework.

Conclusion This study reviewed the compassionate use systems for OOS products in Japan, the United States, and Europe, highlighting current challenges and proposing a sustainable regulatory framework for future practice.

Keywords Out-of-specification product, Autologous regenerative medicine, Clinical trial, Good manufacturing practice, Expanded access program, Compassionate use,, Japan, Food and drug administration, European medicines agency, Regulatory framework

†Masao Sasai and Yayoi Kitawaki have contributed equally to this work.

*Correspondence:
Kiyoshi Okada
okada.kiyoshi.med@osaka-u.ac.jp
[1] The University of Osaka Hospital, Osaka, Japan
[2] The Japanese Society for Regenerative Medicine, Tokyo, Japan
[3] Novartis Pharma K.K, Tokyo, Japan
[4] Forum for Innovative Regenerative Medicine, Tokyo, Japan
[5] National Center for Child Health and Development, Tokyo, Japan
[6] Department of Ophthalmology, Graduate School of Medicine, The University of Osaka, Osaka, Japan
[7] Institute of Science Tokyo, Tokyo, Japan
[8] Department of Cardiovascular Surgery, Graduate School of Medicine, The University of Osaka, Osaka, Japan
[9] National Institute of Health Sciences, Kanagawa, Japan
[10] Terumo Corp, Kanagawa, Japan
[11] Japan Tissue Engineering Co, Ltd, Aichi, Japan
[12] Nipro Corp, Osaka, Japan
[13] Department of Medical Innovation, The University of Osaka Hospital, 2-15, Yamadaoka, Suita, Osaka 565-0871, Japan

Background

In recent years, cell therapy products are expected to provide new treatments for diseases that cannot be treated with conventional pharmaceuticals. In particular, the development and approval of autologous cell-processed products [1–5], which are derived from the cells of the patient, have advanced the field of regenerative medicine [6–8]. Products such as human cellular and tissue-based therapies rely on variable-quality patient-derived tissues [9], leading to the occasional production of out-of-specification (OOS) products [10]. In the case of autologous cell-processed products, collecting the raw materials may not be possible owing to the serious condition of the patient. In addition, the deterioration of the condition of the patient may not allow for manufacturing delays. In the United States and Europe, in such cases, with the consent of the patient and confirmation from the attending physician and marketing authorisation holder (MAH) regarding the expected safety and efficacy, OOS products are provided [11–13]. The safety of patients provided with these OOS products has been reportedly not significantly different from that of commercial products in the United States, United Kingdom, Italy, and Japan [11–16]. The safety of chimeric antigen receptor T-cell (CAR-T) formulations has been reported in terms of the incidence of cytokine release syndrome (CRS) (Grade 3–4) and immune effector cell-associated neurotoxicity syndrome (ICANS) (Grade 3–4) in patients who used OOS and commercial products. Reports from the United States show 21% (95% confidence interval [CI]: 9.0–38.9%) versus (vs.) 15% (95% CI: 10.2–20.1%) and 15% (95% CI: 5.1–31.9%) vs. 8% (95% CI: 4.7–12.5%), respectively, in paediatric patients with acute lymphoblastic leukaemia (ALL) (33 patients vs. 212 patients) [11], and reports from Italy show 0% vs. 3% ($p=1$) and 3% vs. 9% ($p=0.451$), respectively, in patients with diffuse large B-cell lymphoma (DLBCL) (11 patients vs. 33 patients) [13]. Another report from the United States shows 3% vs. 0% and 19% vs. 36%, respectively, in patients with relapsed/refractory (R/R) LBCL (36 patients vs. 25 patients) [14]. Reports from the United Kingdom show 15.4% vs. 6.9% ($p=0.50$) and 7.7% vs. 10.3% ($p=0.72$), respectively, in patients with large B-cell lymphoma (LBCL) (13 patients vs. 38 patients) [15], and reports from Japan show 13.0 and 4.3%, respectively, in patients with R/R LBCL (23 patients) [16]. In the United Kingdom, even after remanufacturing, the commercial product did not meet standards, and hence, the OOS product was provided [15]. Furthermore, studies on these CAR-T formulations have revealed that no difference was observed in progression free survival between those using OOS and commercial products; for example, a report from the United States showed best overall response or complete response of 94% (95% CI: 79.2–99.2%) vs. 84% (95% CI: 78.3–88.8%) in ALL paediatric patients (33 patients vs. 212 patients) [11]; another report from the United States showed 1-year OS 85% vs. 70% in ALL paediatric patients (24 patients vs. 161 patients) [12]; a report from Italy showed 1-year progression free survival (PFS) 45.5% vs. 36.4% ($p=0.899$) in patients with DLBCL (11 patients vs. 32 patients) [13]; a report from the United States showed 1-year overall survival 62% (95% CI: 43–77%) vs. 76% (95% CI: 54–88%) in patients with R/R LBCL (36 patients vs. 25 patients) [14]; a report from the United Kingdom showed 1-year PFS 46.2% vs. 41.4% ($p=0.40$) [15]; and a report from Japan showed 3-months BOR 46.7% in patients with R/R DLBCL (15 patients) [16], suggesting that OOS products have a certain degree of efficacy [12–16].

Although MAHs strive to minimise the need for OOS use through improved manufacturing methods, complete elimination remains unattainable with the existing standards [17]. In Japan, OOS products are currently supplied under clinical trial frameworks, which are primarily designed to collect data for drug approval. This use deviates from the original intent of clinical trials, which are conducted to collect data regarding new drugs or changes to approved medical products, and creates significant administrative burdens for medical institutions and MAHs, including maintaining and managing clinical trials that require non-simplified, uniform procedures, reporting information, and responding to Institutional Review Board (IRB) reviews.

Regulations regarding the provision of OOS products in the United States

In the United States, the available OOS products fall under the compassionate use category within the expanded access program (EAP) [18]. The EAP allows the provision of investigational drugs to patients through the submission of an Investigational New Drug (IND) application to the Food and Drug Administration (FDA). The main purpose of the EAP is to expand access to investigational drugs outside of clinical trials for patients with serious and life-threatening diseases or conditions for which no alternative treatments are available. Unlike general clinical trials, the EAP is not designed to collect safety and efficacy data.

For the provision of OOS products through the EAP, the protocol and informed consent form (ICF) must first be reviewed and approved by the IRB. Before administration, the treating physician must obtain the consent of the patient for using the approved ICF.

An example of the EAP in action is its application regarding Tisagenlecleucel in the United States. Under the EAP, if a product does not meet shipping

specifications, the treating physician can request the provision of an OOS product from the MAH. The MAH may supply the OOS product under a clinical label through an IND but only after confirming that the protocol is being applied at the facility and that the OOS product can be provided following a risk assessment. Under EAP, OOS products are available to patients who meet the following criteria:

1. The patient must be prescribed an OOS product the use of which aligns with the approved indication.
2. The patient is unable to receive commercially available products due to failure to meet shipping specifications.
3. No specific safety concerns related to the manufacturing or shipment of the OOS product exist.

Patient safety monitoring and follow-up for OOS product administration are conducted in accordance with the Risk Evaluation and Mitigation Strategies established for commercial products. Safety information, including reports of severe adverse events, pregnancies, and other pre-specified events, was collected by physicians and submitted to the MAH during and after the protocol-specified follow-up period. Table 1 provides the examples of OOS products supplied under the EAP.

Table 1 Examples of OOS products provided under EAP

No	Product/responsible party	Summary	ClinicalTrials.gov identifier
1	Tisagenlecleucel/Novartis Pharmaceuticals	Managed Access Program (MAP) to provide access to tisagenlecleucel, for patients with acute lymphoblastic leukaemia (ALL) or diffuse large B-cell lymphoma (DLBCL) with out-of-specification leukapheresis product or manufactured tisagenlecleucel, which is otherwise out-of-specification for commercial release	NCT03601442
2	Axicabtagene ciloleucel/Kite, A Gilead Company	The goal of this study was to provide access to axicabtagene ciloleucel for patients diagnosed with a disease approved for treatment with axicabtagene ciloleucel, which is otherwise out-of-specification for commercial release	NCT05776160
3	Brexucabtagene autoleucel/Kite, A Gilead Company	The goal of this study was to provide access to brexucabtagene autoleucel for patients diagnosed with a disease approved for treatment with brexucabtagene autoleucel, which is otherwise out-of-specification for commercial release	NCT05776134
4	Ciltacabtagene autoleucel/Janssen Scientific Affairs, LLC	The purpose of this expanded access program (EAP) was to provide ciltacabtagene autoleucel (cilta-cel) that does not meet the commercial release specifications of CARVYKTI and is not available via the local health care system in the country where the treatment was requested	NCT05346835
5	Lisocabtagene maraleucel/Juno Therapeutics, a Subsidiary of Celgene	This is an EAP that will be conducted at sites qualified and approved to treat patients with lisocabtagene maraleucel. When the manufactured lisocabtagene maraleucel does not pass all tests, it is called non-conforming lisocabtagene maraleucel. The EAP will be used to allow participants to receive non-conforming lisocabtagene maraleucel only if the potential benefit is better than the potential risk. This EAP is restricted to those patients who were prescribed lisocabtagene maraleucel as part of their routine care. Patients will first receive a lymphodepleting chemotherapy regimen and will then be treated with non-conforming lisocabtagene maraleucel as the treatment plan	NCT04400591
6	Idecabtagene vicleucel/Celegene	This study was designed to evaluate the safety and efficacy of non-conforming idecabtagene vicleucel (ide-cel) in participants with multiple myeloma per the approved prescribing information. This is an EAP to be conducted at Risk Evaluation and Mitigation Strategies qualified sites approved for commercial administration of idecabtagene vicleucel and where the EAP is authorised to be conducted for use of non-conforming idecabtagene vicleucel. Non-conforming idecabtagene vicleucel is idecabtagene vicleucel that does not meet commercial release specifications but may be acceptable for use as an investigational product in the EAP setting	NCT04771078

Regulations regarding the provision of OOS products in Europe

In the European market, OOS products are provided to patients as commercial products in accordance with the EU guidelines on manufacturing management and quality control standards for Advanced Therapy Medical Products (ATMPs) [19] as outlined in *EudraLex Volume 4 Part IV* [20].

Under this scheme, OOS product administration is justified when necessary to avoid an imminent and serious risk to the patient. This decision considers the lack of alternative options and the consequences of withholding the cells or tissues contained in the product. Upon the request of a treating physician, the MAH conducts a risk assessment and provides the findings to the physician. If the treating physician requests an OOS product batch considering the specific condition of the patient and the risk assessment, the MAH may provide the product. The MAH must also document the acceptance of the product by the treating physician. The patient must be informed that an OOS ATMP will be administered, with the specific information provided as determined by national legislation [21].

In case of the administration of an OOS product, the MAH must notify the supervisory authority (responsible for granting manufacturing authorisations) and the European Medicines Agency (EMA), which oversees the scientific evaluation and monitoring of ATMPs. In addition, the MAH is required to submit a quality defect report to the competent authority and EMA within 48 h of providing the OOS product. Safety monitoring and follow-up for OOS products adhere to the same pharmacovigilance requirements as regularly marketed products, alongside any additional obligations specific to ATMPs.

The Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-operation Scheme (PIC/S) GMP guidelines address the handling of substandard products in the context of ATMPs. Relevant provisions from the PIC/S Guide to GMP Annex 2A (Sects. 6.11–6.13) [22] include the following:

Section 6.11: Where authorised by national law, the administration of a product that does not meet the release specification, might be performed under exceptional circumstances (such as when no alternative treatment that would provide the same therapeutic outcome is available and the administration of the failed products could be lifesaving).

Section 6.12: In cases, referred to in point 6.11, where product does not meet release specifications, the responsibility and decision of treating the patient are solely of the treating physician and are beyond the remit of this PIC/S annex. The Authorised Person, the MAH, and the Sponsor of the clinical trial should consider the following when providing the product: The treating physician should provide in writing a rationale and request to the Authorised Person and MAH

(A) Batch manufacturing records and documentation provided to the treating physician should clearly state that the batch has failed the release specifications and describe the parameters that have not been met.
(B) When responding to the request of a treating physician, the MAH should provide its evaluation of the product administration risks. However, the administration of the finished product that does not meet release specifications is the sole decision of the physician.
(C) The Authorised Person (or delegate) should report the supply of the product to the relevant Competent Authorities on behalf of the MAH in accordance with their legal obligations.

Section 6.13: The clinical trial Sponsor or MAH should have procedures in place that describe the steps to be taken if the product does not meet release specifications but may be still released to facilitate treatment. Individual cases that do not meet release specifications may be addressed through lot-by-lot release programmes and specific case-by-case, risk-based assessments, where such programs exist within national law.

Herein, this report evaluated the current challenges of providing OOS products in Japan, compared the systems in the United States and Europe, and proposed a new framework for sustainable compassionate use.

Comparison of regulations for the provision of OOS products in the three regulatory authorities

First, we present a comparative table that supplements the understanding of the current situation regarding the provision of OOS products in Japan compared to the United States and European regulatory information mentioned above (Table 2). This table outlines the legal handling of OOS products, the mechanism of provision, eligible patients, and responsibilities of MAH, treating physicians, and medical institutes. In the latter part of this report, we explain the status of product approval and protocol for handling OOS products in Japan and how this method lacks social continuity. We then compare the

Table 2 Comparison of regulatory mechanisms for the provision of OOS products in the regions of the United States, European Union, and Japan

	United States	European Union	Japan
Legal handling of the OOS product	Unapproved product	Commercial product	Unapproved product
Regulatory mechanism of OOS product provision	Expanded sccess	GMP guidelines on exceptional release of OOS ATMPs	Clinical trial
Eligible patients	No specific requirements exist for defining eligible patients for providing OOS products for ethical purposes Expanded access may be appropriate when all the following apply: Patients have a serious or immediately life-threatening disease or condition No comparable or satisfactory alternative therapy exists to diagnose, monitor, or treat the disease or condition Patient enrollment in a clinical trial is not possible Potential patient benefit justifies the potential risks of treatment	Considering the alternative options for the patient and the consequences of not receiving the cells/tissues contained in the product, OOS product administration is necessary to avoid an immediate significant hazard to the patient	In principle, the target patients for clinical trials are those defined for the purpose of collecting data for regulatory approval. No specific requirements exist for defining eligible patients for clinical trials aimed at providing OOS products for ethical purposes
Responsibilities of the HAs	FDA will review a treatment IND/Protocol submitted by a physician or company and authorise the use of the OOS product FDA supervises it in accordance with Expanded Access regulations	Supervisory Authority and EMA requires the MAH to report each OOS provision (within 48 h from the supply) EMA will inform the Committee for Advanced Therapies Rapporteurs of each authorised OOS product. If a trend is detected, the need for regulatory actions will be considered	PMDA will review a CTN of OOS trial submitted by the MAH and authorise the use of the OOS product. The HA does not request a report for each OOS provision PMDA supervises it in accordance with GCP
Responsibilities of the MAH	Submit Treatment IND/Protocol to FDA Follow-up of the patient who received the OOS product in accordance with REMS Report safety information to the HA in accordance with IND requirements	Establish standard operating procedures for providing OOS products. OOS products may be provided only if the requirements of the guidance are met Submit a Quality Defect report to the HA Conduct pharmacovigilance activities in the same manner as those for commercial products	Submit a CTN of OOS trial to PMDA Conduct an OOS trial in accordance with GCP, evaluate the safety and efficacy of OOS products, and report safety information to the HA
Responsibilities of treatment physicians	Confirm patient eligibility Request the MAH to provide the OOS product Obtain patient IC Monitor and follow-up the patient according to the treatment protocol Report safety information to the MAH and HA according to IND requirements	Confirm patient eligibility Request the MAH to provide the OOS product Obtain patient IC Monitor and conduct patient follow-up Report safety information to the MAH and HA (same with that required for commercial products)	Confirm patient eligibility Request the MAH to provide the OOS product Obtain patient IC Monitor and follow-up the patient according to the clinical trial protocol Report safety information to the MAH and HA according to GCP requirements
Responsibilities of medical institutes	Conduct EC review for the use of the OOS product to the patient (including the protocol and ICF)	Conduct EC review for the use of the OOS product to the patient (including the ICF)	Conduct IRB review for conducting an OOS trial (including the protocol and ICF) Conduct an OOS trial in accordance with GCP

ATMP Advanced therapy medicinal product, *CTN* Clinical Trial Notification, *EC* Ethical Committee, *EMA* European Medicines Agency, *FDA* US Food and Drug Administration, *HA* Health Authority, *ICF* Informed Consent Form, *IND* Investigational New Drug, *IRB* Institutional Review Board, *PMDA* Pharmaceuticals and Medical Devices Agency, *MAH* Marketing Authorisation Holder

methods used in other regions, consider their advantages and disadvantages, and present a new framework.

Current state and challenges of providing OOS products in Japan

Approved regenerative medicine and OOS products

As of November 2024, 21 regenerative medicine products have been granted approval in Japan (Table 3), 13 of which are derived from autologous tissues [23–35]. Among these, six products allow the provision of OOS products through clinical trials (Table 4), including four chimeric antigen receptor-T-cell therapies, one autologous skeletal myoblast sheet, and one autologous bone marrow mesenchymal stem cell therapy. When providing OOS products, MAHs conduct risk assessments to confirm the safe administration of products and ensure that patient consent is obtained prior to treatment. The safety profile of OOS products is assumed to be comparable to that of approved products, and no additional risks are anticipated.

- *Reality of providing OOS products and points to consider*:

  OOS products are supplied at a certain frequency owing to the inherent variability in their production. These products are only provided under unavoidable circumstances, such as when no other treatment options are available [12, 36]. To ensure that the provision of OOS products is meaningful for patients, their needs and risks must be thoroughly evaluated in advance (Fig. 1).

  Ensuring safety is paramount when providing OOS products. Products that fail to meet safety standards, such as sterility tests, microbial tests, and visual inspection of appearance, should not be administered. In addition, the decision to administer OOS products must be supported by a reasonable expectation of efficacy. This expectation should be grounded in the information available for each product.
- *Challenges in providing OOS products during clinical trials*:
  As previously mentioned, OOS products in Japan are currently provided through clinical trials, in compliance with the GCP Ministerial Ordinance. For approved products, activities such as sales, Good Vigilance Practice (GVP), and Good Post-marketing Study Practice (GPSP) are conducted based on the manufacturing and sales of regenerative medicine products. Clinical trial responsibilities must be handled alongside these activities.

Clinical trial challenges can be broadly categorised into two types: "direct challenges" and "indirect challenges". The direct challenges are those faced in clinical trials for OOS products, whereas the indirect challenges are those expected to have a negative effect on medical institutions and MAHs as a result of conducting clinical trials of OOS products.

A Direct challenges

1. Medical institutions providing regenerative medicine products must maintain a GCP-compliant clinical trial implementation system for the provision of OOS products. As market penetration and product expansion increase, the associated costs and personnel burden for manufacturers and medical institutions also rise. The increased workload, particularly at medical institutions, can limit the capacity to accept new clinical trials.

   - Clinical trial target facilities: All medical institutions are included in clinical trials because of the specific facility requirements for each product. The number of facilities and personnel is limited, and transferring patients to another institution when an OOS product is required is challenging.
   - Dealing with clinical trials at medical institutions: Institutions must establish and maintain a permanent clinical trial implementation system to accommodate potential OOS product provision. This includes securing clinical trial staff, handling procedures such as IRB reviews, conducting evaluations, and entering data according to clinical trial protocols.
   - Clinical trial period: The trial must continue indefinitely, as long as the product remains on the market. These trials are not intended to support applications for the approval of partial changes to product specifications in the future.

2. Medical institutions and MAHs must establish and maintain dual implementation systems, that is, one for clinical trials and one for regular product use. Operating both systems in parallel poses challenges for medical co-operation and safety. For example, the following cases can be considered:

   - When an OOS product is provided, its planned use as a regular product changes to a clinical

Table 3 List of approved regenerative medicine in Japan

Approval date	By approval	MAHs	Brand name	Common name	Origin of ingredients	Provision of non-standard products
2007/10/29	Approval	Japan Tissue Engineering Co., Ltd	JACE	Human (autologous) epidermis-derived cell sheet	Autologous	No
2012/7/27	Approval	Japan Tissue Engineering Co., Ltd	JACC	Human (autologous) epidermis-derived cell sheet	Autologous	No
2015/9/18	Approval	JCR Pharma Co., Ltd	Temcel HS Injection	Human (allogeneic) bone marrow-derived mesenchymal stem cells	Allogeneic	NA
2015/9/18	Conditional time-limited approval	Terumo Corporation	Heart Sheet*	Human (autologous) skeletal muscle-derived cell sheet	Autologous	Yes (clinical trial)
2018/12/28	Conditional time-limited approval	Nipro Corporation	Stemirac for Injection	Human (autologous) bone marrow-derived mesenchymal stem cells	Autologous	Yes (clinical trial)
2019/3/26	Approval	Novartis Pharma K.K	Kymriah Suspension for Intravenous Infusion	Tisagenlecleucel	Autologous	Yes (clinical trial)
2019/3/26	Conditional time-limited approval	AnGes Inc	Collategene Intramuscular Injection 4 mg*	Beperminogene Perplasmid	Others (hHGF expression plasmid DNA)	NA
2020/03/19	Approval	Novartis Pharma K.K	Zolgensma Intravenous Infusion	Onasemnogen abeparvovec	Others (genetically modified adeno-associated virus)	NA
2020/03/19	Approval	Japan Tissue Engineering Co., Ltd	Nepic	Human (autologous) limbal derived corneal epithelial cell sheet	Autologous	No
2021/01/22	Approval	Gilead Sciences Inc	YESCARTA Intravenous Drip Infusion	Axicabtagene ciloleucel	Autologous	Yes (clinical trial)
2021/03/22	Approval	Celgene Corporation	Breyanzi Suspension for Intravenous Infusion	Lisocabtagene maraleucel	Autologous	Yes (clinical trial)
June 11, 2021	Approval	Japan Tissue Engineering Co., Ltd	Ocural	Human (autologous) oral mucosa-derived epithelial cell sheet	Autologous	No
June 11, 2021	Conditional time-limited approval	Daiichi Sankyo Co., Ltd	Delytact Injection	Teserpaturev	Others (genetically modified herpes simplex virus type 1)	NA
2021/9/27	Approval	Takeda Pharmaceutical Company Limited	Aloficel Injection	Darvadstrocel	Allogeneic	NA
2022/01/20	Approval	Hirosaki Lifescience Innovation, Inc	Sakracy	Human (autologous) oral mucosa-derived epithelial cell sheet using human amniotic membrane substrate	Autologous	NA
2022/01/20	Approval	Bristol-Myers Squibb K.K	Abecma Intravenous Infusion	Idecabtagene vicleucel	Autologous	Yes (clinical trial)
2022/9/26	Approval	Janssen Pharmaceutical K.K	Carvykti Suspension for Intravenous Infusion	Ciltacabtagene autoleucel	Autologous	Under consideration

Table 3 (continued)

Approval date	By approval	MAHs	Brand name	Common name	Origin of ingredients	Provision of non-standard products
2023/03/17	Approval	Japan Tissue Engineering Co., Ltd	JACEMIN	Melanocyte-containing human (autologous) epidermis-derived Cell Sheet	Autologous	No
2023/03/17	Approval	Aurion Biotech Japan LLC	Vyznova	Neltependocel	Allogeneic	NA
2023/6/26	Approval	Novartis Pharma K.K	Luxturna Injection	Voretigene neparvovec	others (genetically modified adeno-associated virus)	NA
2024/7/31	Conditional time-limited approval	SanBio Company Limited	AKUUGO	Vandefitemcel	Allogenic	NA

NA Not applicable

* The conditional and time-limited approval of Collategene was withdrawn in June 2024, and the conditional and time-limited approval of Heart Sheet was withdrawn in July 2024

Table 4 List of clinical trials for the provision of OOS products in Japan

No	Common name	Overview of the study	Target patients	Source
1	Human (autologous) skeletal muscle-derived cell sheet	A multicentre exploratory study on the quality of Heart Sheet among patients who met the selection criteria	Patients with severe heart failure due to chronic ischaemic heart disease	UMIN000029824
2	Tisagenlecleucel	Part 1 will evaluate the safety and efficacy of tisagenlecleucel in the target patients, consistent with the regulatory approved indications listed in the tisagenlecleucel prescribing information in each country/region. Part 2 will evaluate the safety and efficacy of tisagenlecleucel in patients with relapsed/refractory (r/r) acute lymphoblastic leukaemia (ALL) and r/r non-Hodgkin lymphoma (NHL)	Indications for use in the prescribing information: (Part 1: paediatric/young adult patients with r/r B-cell ALL and adult patients with r/r large B-cell lymphoma (including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma); Part 2: patients with r/r ALL and r/r NHL	jRCT1080224903
3	Human (autologous) bone marrow-derived mesenchymal stem cells	The purpose of this study is to administer OOS Stemirac Injection as a compassionate treatment to patients with traumatic spinal cord injury who are unable to receive Stemirac Injection because it does not meet some of the in-process control specifications and shipping specifications, and to obtain efficacy and safety data	Patients with traumatic spinal cord injury	jRCT2013210056
4	Axicabtagene ciloleucel	The clinical trial aims to allow patients who are scheduled to be treated with axicabtagene ciloleucel to be administered the OOS product on compassionate grounds if the product they are receiving does not meet the specifications	Patients who meet the requirements of the package insert (diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, transformed follicular lymphoma, high-grade B-cell lymphoma)	jRCT2013210008
		To access the OOS product and evaluate its safety in adult individuals with a diagnosis of an approved indication listed in the package insert	Patients who meet the requirement of the package insert (relapsed or refractory large B-cell lymphoma)	jRCT2033230370
5	Lisocabtagene maraleucel	To assess the safety of OOS products	Patients who meet the requirement of the package insert (relapsed or refractory large B-cell lymphoma)	jRCT2053200162
6	Idecabtagene vicleucel	To evaluate the safety of OOS products	Patients who meet the requirement of the package insert (adult subjects with relapsed or refractory multiple myeloma)	jRCT2053220006

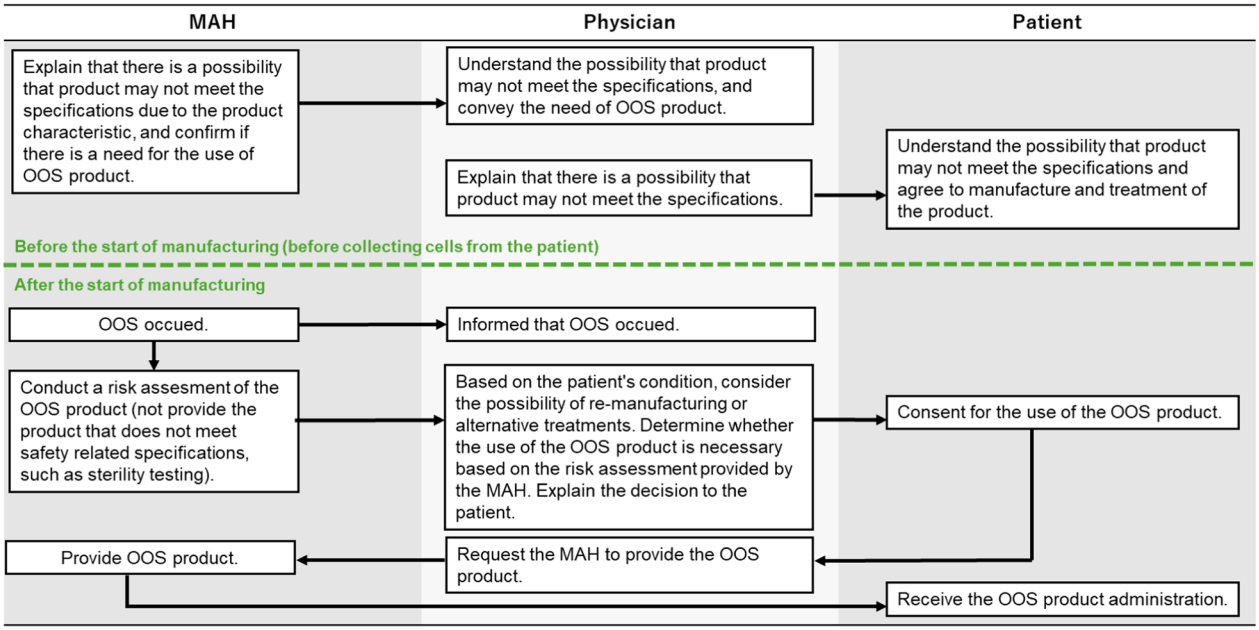


Fig. 1 OOS product provision flow. The MAH establishes an evaluation system for OOS products, conducts a risk assessment for each OOS product, and provides the assessment result to the physician. If the OOS product does not meet safety-related specifications, such as sterility testing, it is not provided. The physician considers the possibility of remanufacturing or alternative treatment based on the condition of the patient, and if it is determined that it is medically necessary and the patient wishes to receive the OOS product, the physician requests the MAH to provide the OOS product based on the individual risk assessment provided by the MAH

trial use, requiring additional involvement from clinical trial management departments. This shift may confuse medical staff.

- Similarly, within MAHs, the primary responsibility shifts from the sales department to the clinical development department, complicating operations.

3. From the perspective of the patient, administrative procedures required for clinical trials can delay treatment. These delays may arise from the need to obtain consent, schedule product delivery, or meet clinical trial-specific requirements, such as additional blood tests or washout periods for previous treatments, which are part of routine medical practice. Such procedures may disadvantage patients by postponing administration or introducing additional burdens.

B Indirect challenges

1. For MAHs, the cost and personnel burden associated with OOS product provisions limit the resources available for developing new drugs, hindering original research efforts.
2. Continued clinical trial requirements for OOS product provision impose significant burdens on MAHs, complicating the commercialisation of regenerative medicine products.
3. Requiring clinical trials for OOS product provision may raise concerns to foreign MAHs about the attractiveness of the Japanese market. This could influence investment decisions and reduce market participation.

These challenges create distortions and inefficiencies in medical procedures at medical institutions and MAH activities. Such actions because of clinical trial requirements could slow the development of regenerative medicine in Japan, reduce its international competitiveness, and limit the access of Japanese patients to innovative regenerative medicine products.

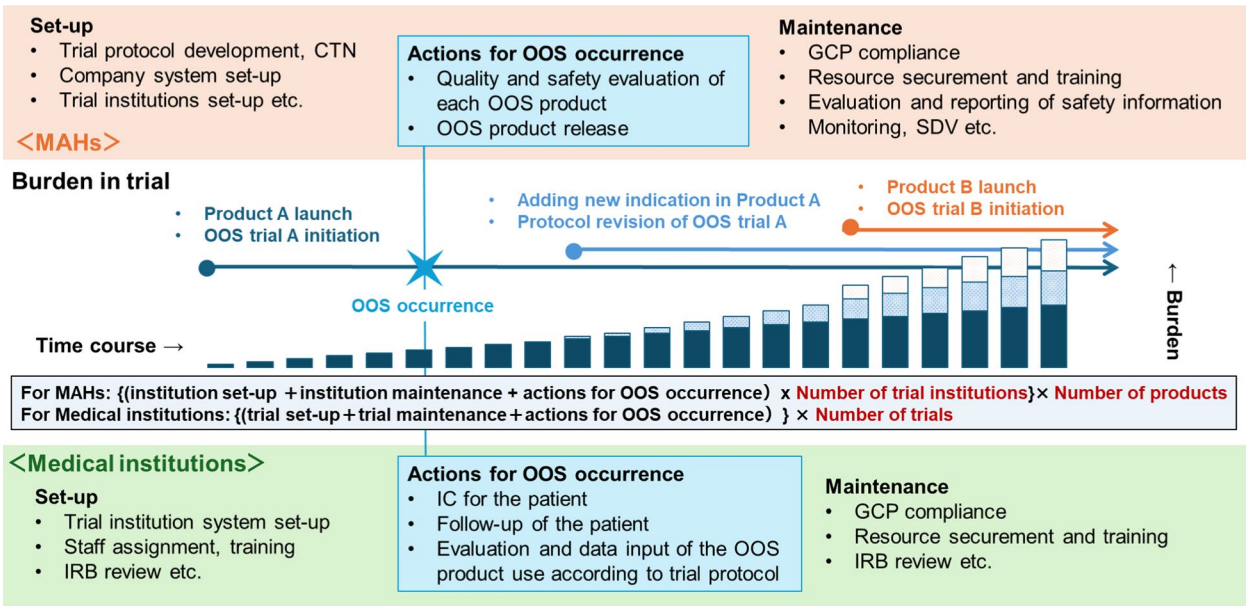
Proposed framework for sustainable compassionate use in Japan

We conducted interviews with stakeholders, such as medical institution staff or MAHs that provided commercial products and conducted clinical trials for OOS products, to examine the effect of simplifying activities and procedures related to ensuring data reliability to reduce the burden of clinical trials.

Interviews with six staff members from three medical institutes revealed concerns about maintaining a clinical trial for each product, as shown in Fig. 2. Four MAHs for regenerative medicine products also expressed concern that setting up and maintaining a clinical trial for the provision of OOS products would be an unsustainable approach.

In interviews with experts on FDA or EMA regulations, publicly available regulatory information and whether or not discussion was ongoing about changing the system regarding the provision of OOS products could not be confirmed. Similarities were identified between the FDA and EMA regarding the compassionate use of OOS products, such as targeting patients with serious diseases and conditions and providing treatment opportunities in situations where no other treatment options are available. However, differences were also found between the two authorities, in that the FDA requires implementation in INDs that require FDA approval, whereas the EMA requires reporting by the authorities but allows exceptional shipments of approved products. Considering the design of the Japanese system with reference to these and that the Japanese notification to the PMDA is based on a system design aiming at approval and insurance reimbursement, aiming for the European model for patient access was considered better.

- *Rational simplification of clinical trials*:
  A rational simplification of the current clinical trial system was explored to reduce burdens on medical institutions and MAHs while maintaining proper oversight and safety. Key considerations included ensuring patient safety and the reliability of the clinical trial data.
- *Ensuring the safety of patients administered OOS products*:
  The requirements for the facilities and medical personnel administering OOS products align with those for commercially available products. Administration by trained medical staff at a facility meeting the established requirements for the relevant regenerative medicine product ensures that safety standards are upheld. In terms of providing safety information to facilities, the patient population receiving OOS products is the same as that for marketed products, and the required safety measures are identical. These safety measures can be implemented effectively by adhering to GVP activities and leveraging the package inserts of marketed products.
  Based on these premises, we considered that meeting the requirements applicable to commercially available products, coupled with robust safety management practices, provide sufficient assurance of patient safety during OOS product administration.



CTN; Clinical Trial Notification, OOS: Out-of-specification, GCP: Good clinical practice, SDV: Source Document Verification, MAH; Marketing authorisation holder, IRB; Institutional Review Board.

Fig. 2 Issues of OOS product provision in clinical trials

- *Reporting safety information on OOS products to authorities and facilities*:
  Regarding defect reporting to authorities, as outlined before, the safety of OOS products is considered equivalent to that of commercially available products. Therefore, defect reporting for OOS products can utilise the same processes applied to commercially available products, including the subjects of reports and reporting deadlines. Similarly, reporting defects to facilities can follow the same procedures established for commercially available products.
- *Handling clinical trial data and ensuring reliability*:
  The purpose of this clinical trial was to support potential partial changes to product specifications in the future. In this context, forgoing stringent measures to ensure the reliability of approval application documents, such as direct inspections of source documents by monitors, is reasonable. If necessary, data collection and handling can be managed similarly to Post-marketing Study activities conducted for commercially available products. Furthermore, waiving the requirement for preparing a clinical trial summary report, as mandated by the GCP Ministerial Ordinance is reasonable.

Based on the above considerations, Table 5 outlines the actions that can or cannot be streamlined through rational simplification of clinical trials. Actions that can be simplified primarily involve processes related to the occurrence and administration of OOS products, such as monitoring source data comparisons, data collection for approval applications, safety information reporting to authorities, and record-keeping. However, certain actions cannot be reduced, particularly those that represent fixed costs irrespective of the frequency of OOS product provisions. These include establishing

Table 5 Consideration of streamlining in clinical trials for provision of OOS products

Timing		MAHs (sponsor)	Medical institutions
Clinical Trials Before starting	Extrusion	*Items that can be streamlined* Preparation of Investigational Brochures (IB) may be substituted with the package inserts *Items that cannot be streamlined* Preparation of clinical trial protocols and informed consent forms Compensation for participants Preparation for clinical trial product management Site setup (medical institution and investigator selection, site training) Clinical Trial Notification (CTN) Clinical trial contract IRB review application preparation Maintenance of records	*Items that can be streamlined* Agreement with IB may be substituted with the package inserts *Items that cannot be streamlined* Agreement to the clinical trial protocol and informed consent form Site setup Clinical trial contract handling IRB review support
Clinical Trials After starting	Permanent	*Items that can be streamlined* Storage of essential documents (case report forms, data obtained in clinical trials, and simplification of storage periods) *Items that cannot be streamlined* Regular confirmation of clinical trial system maintenance Evaluation of safety information, reporting to authorities and medical institutions (annual reporting, sharing of information with other sites) IRB review for protocol revisions, etc Maintenance of CTN monitoring investigators, site staff, and site trial system	*Items that can be streamlined* Maintenance of records (simplification of source documents and retention period) *Items that cannot be streamlined* Maintaining and continuing training of investigators and staff to conduct clinical trials in compliance with protocols and GCP IRB support (ongoing review, protocol revision support, etc.)
	Each time	*Items that can be streamlined* Procedures for converting commercial products to investigational products (product re-labelling) **Collection of case report forms** Handling of subject safety information EDC Verification of source data *Items that cannot be streamlined* **Collection of case report forms** Monitoring Participant eligibility Confirmation of patient consent status Ensuring the safety of participants	*Items that can be streamlined* None *Items that cannot be streamlined* Safety information evaluation, reporting to sponsor

and maintaining clinical trial contracts, IRB review processes related to facility setup, GCP-compliant staff and facility systems, and ongoing IRB reviews.

Even if certain tasks, such as data collection using case report forms for approval applications and source document comparisons, are deemed unnecessary, a significant portion of the workload remains during the initiation and execution of clinical trials. This highlights the inherent limitations of simplifying clinical trials. Furthermore, the reduction in burden achieved through simplification accounts for < 10% of the total cost of a clinical trial. As long as the framework relies on clinical trials, the burdens on companies and medical institutions are only marginally alleviated, even with simplification measures. Therefore, the rational simplification of clinical trials contributes minimally to the sustainability of the current framework for OOS product provision.

As previously mentioned, clinical trials for the compassionate use of OOS products place a burden that impedes new research and development activities for both parties and significantly affects the advancement of new treatments in Japan. Furthermore, some institutions will refrain from adopting new regenerative medicine products owing to the burden of clinical trials required for the compassionate use of OOS products.

The above considerations led to the conclusion that this would not contribute to reducing system load and promoting sustainability, thereby prompting the development of a new framework.

The United States system is similar to the Japanese clinical trial system, and thus, the current challenges will remain. In addition, the EAP framework cannot be accommodated by current Japanese laws and regulations. Therefore, new regulations would be necessary, which could not be immediately applied. In the United States, two pathways, Intermediate-Size Patient Access and Individual Patient Access, are used in parallel. In Japan, no single IND system exists. Therefore, to respond to requests for OOS products for all patients, setting up and maintaining clinical trials at all MAH are necessary. This places a greater burden on the system in Japan than in the United States. However, the European system is an exception for the provision of commercial products, and the burden of conducting clinical trials is greatly reduced, indicating its sustainability. A disadvantage of the European system is the potential weakness in the involvement of regulatory authorities. This concern can be addressed by submitting prior notification to the PMDA regarding provisions of OOS products under the Japanese system, thereby ensuring the proper functioning of operations.

Establishment of a new framework

In order to make the provision of treatment opportunities using OOS products sustainable, we considered a new framework. Although the provision of OOS products to institutions by MAHs is prohibited under Article 65-5 of the PMD Act, we considered that a highly sustainable framework could be created by allowing exceptions only for the provision of autologous regenerative medicine for treatment, based on the European framework (Fig. 3).

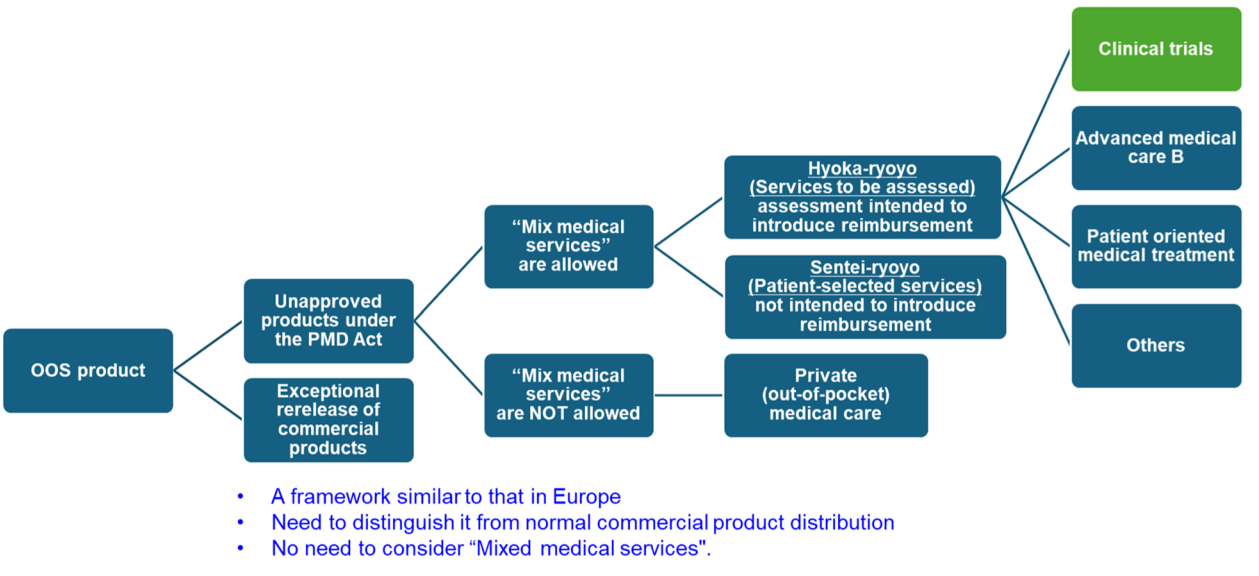


Fig. 3 Order of consideration of the system for supplying OOS products. OOS; Out-of-specification, PMD; Pharmaceutical medical device

Table 6 New framework for ethical provision of OOS products

Items	Proposition
Purpose and objective	Compassionate use for patient treatment
Necessary regulatory compliance	The law needs to be amended to provide exceptions to Article 65–5 of the PMD Act
Legal handling of OOS products	Commercial products
Definition and standards of OOS products that can be provided	Autologous regenerative medicine that have no clearly increased risks compared with that of commercially available products and whose benefits outweigh the risks. Although setting uniform standards is difficult, products that do not meet safety standards, such as sterility, will not be provided
Indications	Patients with serious diseases or conditions for whom alternative treatments are not available and OOS products have been considered to be essential for treatment, with their consent
HA interaction	The requirements for OOS products that may be exceptionally provided are stipulated in the Ministerial Ordinance. MAHs providing OOS products must notify the HA of the applicability of these requirements and the specification items that can be provided for each product
Supply flow of OOS products	MAHs will establish an evaluation system for OOS products, conduct a risk assessment, and provide the physician with the risk assessment. Based on the risk assessment provided by the MAHs, physician will conduct a risk–benefit assessment for each patient and determine whether or not to use the OOS product. Physicians will obtain the patient's consent for using the OOS products and request their provision from MAHs
Monitoring system for the use of OOS products	The appropriateness of using OOS products on patients must be approved by the Ethics Committee (EC) before their administration to patients. The overall flow of using OOS products is reviewed and approved in advance by the EC. As OOS products are required to be provided promptly, no need for review will be required when using individual OOS products, which should be administered at the physician's discretion in accordance with the approved flow
Reports from MAHs	The number of OOS products and doses can be provided as requested by the authorities
Safety information collection and reporting system	As part of safety monitoring activities for commercially available products, a system will be established for collecting, evaluating, and communicating information on OOS products
Safety and efficacy data collection	As with commercial products, post-marketing safety monitoring is required, and the details of the implementation are left to the discretion of each MAHs
Contract between Medical institutions and MAHs	When concluding a contract to adopt commercially products, matters related to OOS products would be also handled

An outline of the new framework is shown in Table 6. The new framework has been designed to clarify the objectives, such as the intended use, methods for legal compliance, background of target diseases, protocol for managing OOS products, the involvement of regulatory authorities, and monitoring processes such as the provision of products and obtaining safety information, as well as implementation of a reporting system. The framework has been designed to be practical and ensure that the content is not detrimental to patients. The process of conveying information to patients and providing the OOS product can be executed in a similar manner as currently done (Fig. 2), which has proven to be effective. The main purpose of the system is the compassionate use of OOS products that can be provided as an exception to Article 65-5 of the PMD Act for patient treatment.

Conclusions

In Japan, the compassionate use of OOS products in autologous regenerative medicine through clinical trials is misaligned with the original objectives of clinical trials. Each approved product requires a distinct approach, creating an excessive burden for both medical institutions and MAHs. This strain impedes new research and development activities for both parties and significantly affects the advancement of new treatments in Japan. Therefore, a sustainable framework for the compassionate use of regenerative medicine products is urgently needed. To address these challenges, the Ministry of Health, Labour and Welfare of Japan established a study committee in February 2024 to consider revising the Pharmaceuticals and Medical Devices Act, with the draft results of its deliberations to be compiled in December 2024. We hope these discussions will pave the way for a more sustainable and reasonable approach to the compassionate use of regenerative medicine products.

Abbreviations

AMED	Japan agency for medical research and development
ATMP	Advanced therapy medicinal products
EAP	Expanded access program
EMA	European medicines agency
FDA	Food and drug administration
GCP	Good clinical practice
GMP	Good manufacturing practice
GPSP	Good post-marketing study practice
GVP	Good vigilance practice
HA	Health authority
ICF	Informed consent form
IND	Investigational new drug
IRB	Institutional review board
JSRM	Japanese society for regenerative medicine
MAH	Marketing authorisation holder
OOS	Out-of-specification
PIC/S	Pharmaceutical inspection convention/pharmaceutical inspection co-operation scheme

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Author contributions
MS and YK contributed to draft writing. AU, KO, YO, NK, TK, HS, SH, KY, YY, HI, and YM contributed to the review and final approval of the manuscript.

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Declarations

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