Compassionate use programs: An overview of the global landscape

By Khoa Bui, Lead Regulatory Consultant

Abstract

Compassionate use serves as a useful pathway to provide access to unauthorized medicines to patients that are otherwise unable to participate in clinical trials, fulfilling an unmet medical need.

These programs vary widely across the globe, from regulatory definition/terminology to submission and safety reporting requirements. For example, some countries may restrict this use to an individual (also referred to as 'named patient'), in which an application needs to be lodged for every patient the healthcare professional wishes to prescribe the unauthorized medicine for; in other cases, some countries do not have any regulatory frameworks for such programs, leading to gaps in access to critical care.

This white paper explores the global landscape of compassionate use, highlighting similarities and differences between programs across different countries.

1. Introduction

Access to unauthorized medicines is typically restricted to their use in clinical trials, which recruits volunteers to test these medicinal products on in order to collect safety and efficacy data to support its push towards market authorization. Compassionate use, also known as expanded access (along with other names), is a regulatory pathway that allows patients with serious or life-threatening conditions to access investigational medical products outside of clinical trials when no satisfactory approved therapies are available. In some cases, these overlap with post-trial access programs, which serve on the same basis of compassionate use but are specific to patients that have been part of the clinical trial as part of continued treatment.

These programs serve as a vital bridge between clinical research and patient care, offering hope and potential relief to individuals or cohorts who are otherwise out of options. This paper looks to present the current regulatory landscape around compassionate use for the following countries/region, covering regulatory frameworks and application requirements for selected markets across international regions, namely the United States. European Union, Japan, Singapore, South Africa and Venezuela. These markets were selected to highlight both the similarities and differences across programs, from scope of application to regulatory expectations by their respective governing bodies.

2. Methodology

Information for this review was covered by the review of official legal documents, regulatory guidelines and submission portals of the countries in scope through Cortellis Regulatory Intelligence (CRI) to review all compassionate use-related documentation published by each regulatory authority.

Markets: United States, European Union, Japan, Singapore, South Africa and Venezuela.

Topic: 'Compassionate use', 'expanded access', 'post-trial access', 'individual use'.

Date Range: 31 August 2000 to 31 August 2025.

Document types in scope: Circular, Checklist, Decision, Decree, Directive, Guidelines, Laws, Regulation, Resolution, Order, Ordinance, Standard Operating Procedure, Federal Register Announcement, Form, Information Note, Notification, Report.

Document types out of scope: Agreement, Citizen Petition, Committees and Working Groups, Communication, Consultation, Fact Sheet, Inspection Report, Letter, Meeting, Newsletter, Other type, Presentation, Press Release, Product Information.

3. Overview of compassionate use programs

United States

Expanded Access

In the United States, Compassionate Use is known as 'Expanded Access.' Per 21 CFR 312.305(a), the following general criteria must be met for the use of Expanded Access:

1. The patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;

2. The potential patient benefit justifies the potential risks of treatment use, and those potential risks are not unreasonable in the context of the disease or condition to be treated; and

3. Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.

This program allows for the treatment of: 1) individuals; 2) cohorts (intermediate-sized groups); and 3) widespread use (known as treatment INDs), all of which require the above criteria to be met along with additional FDA determinations based on the treatment scenario that applies.

It should be noted that companies may be permitted to charge patients for treatment under Expanded Access if the three circumstances are met:

1. Provide evidence that the drug has a potential clinical benefit that, if demonstrated in the clinical investigations, would provide a significant advantage over available products in the diagnosis, treatment, mitigation, or prevention of a disease or condition;

2. Demonstrate that the data to be obtained from the clinical trial would be essential to establishing that the drug is effective or safe for the purpose of obtaining initial approval of a drug, or would support a significant change in the labeling of an approved drug (e.g., new indication, inclusion of comparative safety information); and

3. Demonstrate that the clinical trial could not be conducted without charging because the cost of the drug is extraordinary to the sponsor. The cost may be extraordinary due to manufacturing complexity, scarcity of a natural resource, the large quantity of drug needed (e.g., due to the size or duration of the trial), or some combination of these or other extraordinary circumstances (e.g., resources available to a sponsor).

Key Definitions (per 21 CFR 312.300)

Immediately life-threatening disease or condition means a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

Serious disease or condition means a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

European Union

Compassionate Use

Per the European Union, compassionate use means to make a medicine available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorised

medicinal product. The medicinal product concerned must either be the subject of an application for a marketing authorisation or must be undergoing clinical trials. Member States may also allow for the provision of unauthorized medicinal products formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility.

Post-trial access

In some cases, patients may continue to receive treatment following the conclusion of a clinical trial on an ethical basis. Post-trial arrangements (i.e., follow-up care and treatment) should be described in the clinical trial protocol to allow for the continued provision of investigational medicinal products to patients, as necessary. However, these provisions do not list an explicit requirement to provide investigational medicinal product after the clinical trial is completed. According to Regulation (EU) No. 536/2014, Annex 1(17)(ae), the protocol needs to include a description of the arrangements for taking care of the subjects after their participation in the clinical trial has ended, where such additional care is necessary because of the subjects' participation in the clinical trial and where it differs from that normally expected for the medical condition in question.

Japan

Compassionate use/expanded clinical trial

Japan models their pathway after the US and the EU, with an emphasis that the product be conducted as a clinical trial. Japan's compassionate use is essentially an expanded clinical trial for the treatment of diseases that are life-threatening and for which there are no effective existing treatments, in which unapproved drugs are provided to patients who do not meet the criteria for participation in clinical trials from a humanitarian standpoint, in order to ensure access by these patients, while balancing the risks and expected therapeutic benefits of the use of the unapproved drug, provided that it does not impede the development of the drug in question. Compassionate use covers the period from late stage of development to listing in the National Health Insurance (NHI)-price list after approval. A verification study should be underway or completed in the development stage. This program is conducted under a clinical trial plan notification submitted separately from ongoing "main" clinical trial.

Costs related to clinical trials are covered by the sponsor, but in expanded clinical trials, it is also permitted to require participating patients to bear a proportionate share of the costs of manufacturing, transporting, managing, and storing the investigational drug, as well as the costs of drugs with the same efficacy (if not covered by medical insurance).

Singapore

Special Access Route (SAR)

Singapore presents access to life-saving therapies for individual patients where there is an unmet medical need, such as in situations where treatment option is absent, and the patient's health will be clinically compromised without treatment with the unregistered therapeutic product. This route also applies to the import of buffer stock of unregistered therapeutic product noted as standard essential medicine per the Ministry of Health Standard Drugs List, which are medicines to be kept in the event of critical need across healthcare facilities.

This named-patient application's purpose is to:

a) import and supply an unregistered therapeutic product which presents a life-saving treatment option to the patient whose condition would be clinically compromised without the requested therapy, and that there is no effective alternative therapy registered in Singapore, or

b) import and supply a novel unregistered therapeutic product which offers a substantive clinical advantage over registered therapies and is expected to provide significant improvement to the patient's clinical outcome.

The buffer stock application's purpose is to:

a) import and supply the unregistered therapeutic product which is a standard essential medicine listed on the Ministry of Health (MOH) Standard Drugs List, to be kept as stocks in hospitals, clinics or nursing homes to meet the critical needs of Singapore's healthcare system, or

b) import and supply the unregistered therapeutic product which is a standard essential medicine listed on the Hospital Pharmacy and Therapeutics List, to be kept as stocks in hospitals to meet the critical needs of the hospitals.

It should be noted that the maximum quantity of each consignment cannot exceed a total of three months' supply per patient based on the recommended dose from the package insert, though exceeding this quantity can be substantively justified based on medical needs. Consignment approval validity is 6 months for the named-patient application and 12 months for buffer stock applications.

South Africa

Access to unregistered medicines for human use

The South African Health Products Regulatory Authority (SAHPRA) covers 'access to unregistered medicines for human use' under section 21 of the Medicines and Related Substances Act, an authorisation may be granted to an unregistered medicine by SAHPRA. The main purpose of this route is to provide access to medicines where conventional therapies have been ruled out, have failed or are unavailable for use. Section 21 authorisations are valid for a maximum of 6 months for each application unless otherwise stated.

This access is further divided into the categories of the following:

1. Individual named patient
2. Bulk stock held by a health establishment
3. Bulk stock held by the holder of a license
4. State procurement
5. Public health emergency

Unregistered medicines may only be sold if authorized by SAHPRA under Section 21 of the Medicines Act, provided there is sufficient justification. SAHPRA may impose conditions on such sales at the time of authorization or later, in accordance with Section 21 and Regulation 29.

Post-trial access, continued access

Before starting a clinical trial, sponsors and researchers should plan for post-trial or continued access (PTA/CA) for participants who benefit from the investigational product. This access should be discussed during informed consent, when appropriate. If PTA/CA is feasible, the trial proposal must explain how it will be provided—such as through a roll-over study or an expanded access program.

Roll-over studies are for eligible participants from the clinical trial to be given continued treatment, whereas expanded access programs serve as a formal pathway for a group of patients with a serious condition and were unable to participate in the clinical trial to access an investigational drug outside of clinical trials when no satisfactory alternatives exist.

Venezuela

Medicines of Service

Venezuela's compassionate use program is known as 'Medicines of Service.' The following categories are defined under Medicines of Service:

- Medicinal product for rare diseases – products indicated for a clinical condition whose frequency is less than 5 in 10,000 inhabitants.
- Medicinal product for tropical and endemic diseases – products indicated for clinical conditions associated with climate and geographical factors specific to the country, of variable and permanent incidence; in which there is little to no offer of a product in the country.
- Medicinal product for compassionate use - products responding to an extreme decision from the prescribing person to treat a patient or a small group of patients who are in severe or incapacitating clinical condition. Not for commercial use.
- Early access medicinal product - products under clinical research phase proposed to extend and/or improve the patient's quality of life when it constitutes a superior therapeutic option to those products in the market. Not for commercial use.
- Medicines intended for national health programs or to address a shortage in marketed products.

The Service Medication status will last for 1 year but can be renewed with another application as needed.

Table 1: Compassionate use program names and features by market

Market	Regulatory Authority	Program Name	Legal Basis / Guidance	Key Features
United States	Food & Drug Administration (FDA)	Expanded Access	21 CFR Part 312 Subpart I	Follows clinical trial framework. Grouped by number of patients treated: Individual, Intermediate, or Treatment IND. Patients could bear some of the costs
European Union	European Medicines Agency (EMA) + Member States	1) Compassionate Use 2) Post-trial access	1) Regulation (EC) No. 726/2004, Article 83 2) Directive 2001/83/EC, Article 5 3) Regulation (EU) No. 536/2014, Annex 1(17)(ae)	Overarching legal framework but Member States must decide how such programs are conducted
Japan	Pharmaceuticals and Medical Devices Agency (PMDA)	Compassionate Use (Expanded Clinical Trial)	Notification: PSB/PED No. 0913/2: Conducting Clinical Trial for Compassionate Use, 13-Sep-2024	Follows clinical trial framework. Company permitted to have patients bear some of the costs
Singapore	Health Sciences Authority (HSA)	Special Access Route (SAR)	Regulation No. S 329, 25-Oct-2024, regulations 5(1)(b)(i) and 51	Only designed for individual named patients or as buffer stock for critical emergencies
South Africa	SAHPRA	1) Access to unregistered medicines for human use (Section 21) 2) Post-trial access	1) Guideline SAHPGL-CEM-S21-02: Section 21 Access to Unregistered Medicines 2) Guideline SAHPGL-CEM-CT-07: Post Clinical Trial Access (PTA) / Continued Access	Broad range of scenarios, company permitted to sell where justified
Venezuela	Institute of Hygiene Rafael Rangel (INHRR)	Medicines of Service	Norm on Medicines of Service, 01-Jul-2015 – Article 9	Broad range of scenarios, including tropical/endemic diseases

4. Submission Process

United States

To utilize the Expanded Access pathway, the company/sponsor (or licensed physician for individual/intermediate-size INDs) must submit an Expanded Access Request to the United States Food & Drug Administration (FDA). This may be submitted in the form of a new IND or a protocol amendment to an existing IND. As such, an IND may go into effect 30 days after FDA receipt of the application or upon earlier notification by the FDA. Per 21 CFR 312.305(b)(2), the expanded access submission must include the following:

1. A cover sheet (Form FDA 1571) meeting requirements of 21 CFR 312.23(a);

2. The rationale for the intended use of the drug, including a list of available therapeutic options that would ordinarily be tried before resorting to the investigational drug or an explanation of why the use of the investigational drug is preferable to the use of available therapeutic options;

3. The criteria for patient selection or, for an individual patient, a description of the patient's disease or condition, including recent medical history and previous treatments of the disease or condition;

4. The method of administration of the drug, dose, and duration of therapy;

5. A description of the facility where the drug will be manufactured;

6. Chemistry, manufacturing, and controls information adequate to ensure the proper identification, quality, purity, and strength of the investigational drug;

7. Pharmacology and toxicology information adequate to conclude that the drug is reasonably safe at the dose and duration proposed for expanded access use (ordinarily, information that would be adequate to permit clinical testing of the drug in a population of the size expected to be treated); and

8. A description of clinical procedures, laboratory tests, or other monitoring necessary to evaluate the effects of the drug and minimize its risks.

IRB approval per 21 CFR 56 is expected to be obtained prior to submission to the FDA, though exceptions apply for cases of emergency treatment, in which they should be notified within 5 days of treatment initiation. Submissions should be made through the Electronic Submissions Gateway (ESG).

Forms

For expanded access, the company/sponsor must submit Form FDA 1571 (IND Application Cover Letter) with all relevant contents alongside Form FDA 1572 (Statement of Investigator).

For licensed physicians looking to submit their own IND, they are encouraged to use Form FDA 3926 (Individual Patient Expanded Access IND Application) but may also opt for Form FDA 1571 and 1572 instead. They should also look to acquire a Letter of Authorization (LOA) from the company/sponsor, though where an LOA is not available, they may submit sufficient information on the Forms for the FDA to assure the product's quality.

European Union

While the European Union sets the legal basis for compassionate use and post-trial access, the implementation, coordination and approval of such programs are managed individually by each Member State according to their own rules and legislation. As such, application requirements and review timelines vary with each Member State. The Member States' competent authorities will inform the Agency of any products they are making available for compassionate use.

However, the European Medicines Agency does provide a list of compassionate use recommendations through their Committee for Medicinal Products for Human Use (CHMP). These recommendations are meant to complement national legislation and are entirely optional. While they do not create any legal frameworks in the Member States, they present useful summaries and opinions on the conditions of use for various products.

Japan

Request by physician to the clinical trial sponsor

Expanded access trials are not a legal obligation and are dependent on the sponsor's willingness to conduct an expanded clinical trial; a doctor may make a request to the sponsor to include their patient(s) in the expanded clinical trial. The doctor should provide explanatory documents (information on the patient, why the patient cannot participate in the conventional clinical trials ongoing, necessity of participation, etc.) as a request to the sponsor to support an expanded access trial. From there, the sponsor will respond on whether the patient may be included (see Form 1 of Notification: PSB/PED No. 0913/2: Conducting Clinical Trial for Compassionate Use, 13-Sep-2024). If the sponsor disagrees with the implementation of an expanded access trial, the doctor may request the Ministry of Health, Labour and Welfare (MHLW) to challenge the sponsor to reconsider by submitting a separate form (see Form 2 of Notification: PSB/PED No. 0913/2: Conducting Clinical Trial for Compassionate Use, 13-Sep-2024) to the MHLW along with the sponsor response (Form 1).

Initiating an expanded access trial

To initiate an expanded access trial, a clinical trial plan notification (CTPN) must be submitted by the sponsor to the PMDA following IRB approval. The expanded access trial is conducted within the framework of a clinical trial and would thereby require the following information to be submitted to the PMDA through the Gateway System:

1. The composition and quantity of the investigational drug (the drug to be used in the clinical trial (investigational drug) and the drug to be used to evaluate the efficacy and safety of the investigational drug)
2. The method of manufacturing of the investigational drug
3. Intended indications of the investigational drug
4. Intended dosage and administration of the investigational drug
5. Purpose, content, and duration of the clinical trial
6. Name and location of the medical institution where the clinical trial will be conducted
7. Name and address of the person establishing the committee that conducts investigations and deliberations on the appropriateness of conducting the clinical trial at the medical institution and other matters related to the clinical trial.
8. Name of the physician (principal investigator) who will oversee operations related to the clinical trial at each medical institution where the clinical trial will be conducted
9. In the case where there is a physician who is assigned to work on the clinical trial under the guidance of the principal investigator, the name of such physician
10. Quantity of investigational drug(s) delivered or obtained at each site where the clinical trial is planned to be conducted
11. Expected number of subjects per medical institution conducting the clinical trial
12. If the investigational drug is to be transferred for a fee, the reason for the transfer
13. In cases where the person requesting the clinical trial does not have an address in Japan, name and address of the person appointed from among those who have an address in Japan (including a representative of a foreign corporation having an office in Japan) and is authorized to request the clinical trial on behalf of the person requesting the clinical trial, in order to have the person take necessary measures to prevent the occurrence or spread of health hazards due to the investigational drug
14. In the case of commissioning a physician to interpret the protocol or to coordinate other details of the clinical trial, the name of the physician
15. In the case where a committee consisting of several physicians is entrusted with the task of interpreting the protocol and coordinating other details of the clinical trial, the names of the physicians who comprise the committee
16. In the case where the person who intends to request a clinical trial outsources all or part of the work related to the request and management of the clinical trial, the name and address of the person who outsources such work and the scope of such work to be outsourced
17. In the case where the site entrusts a part of the services related to the conduct of the clinical trial, the name and address of the person entrusted with the services and the scope of the services to be entrusted

Investigational drugs whose active ingredient has not been approved in Japan or whose dosage form is new, or which is a new fixed-dose combination drug can be initiated after 30 days following initial submission of the notification if there are no objections. Otherwise, these trials can be initiated after 14 days following submission.

Singapore

The Special Access Route (SAR) is initiated by the importer (licensed hospital, clinic, nursing home, pharmacy, or company acting on behalf of a health institution) of the product to the Pharmaceuticals & Biologics Branch (PBB), Product Evaluation & Registration Division, Health Sciences Authority.

It should be noted that if a company is acting on behalf of a hospital, clinic or nursing home to import medicinal products, they must have a valid Therapeutic Products Importer's License (TPIL) prior to carrying out any import activity, and a Therapeutic Products Wholesaler's License (TPWL) to supply said product to the parties of interest. A licensed hospital, clinic, or nursing home, as well as licensed retail pharmacies, are not required to own either license prior to import.

An application can be lodged through the following link: https://go.gov.sg/sar-npb-appl-form. The two key documents are expected in the application:

1. Form: HSA - Application for Consignment Approval of an Unregistered Therapeutic Product for Patient's Use, Sep-2024

2. Evidence that supports the use of an unregistered medicine

South Africa

Section 21 Applications

Applicants looking to pursue compassionate use per Section 21 should submit the application with their prescribed fees and the following information as noted in Regulation 29(2) of General Regulations Made in Terms of the Medicines and Related Substances Act, 1965 (Act 101 of 1965), No. R. 859, 25-Aug-2017:

1. Completed application form

2. Product brochure containing relevant chemical, pharmaceutical, pre-clinical pharmacological and toxicological data and where applicable, human or animal pharmacological and clinical data with the medicine concerned

3. witnessed informed consent document, where applicable

4. details of registration or pending registration of the medicine with any other regulatory authority, if available

5. evidence of GMP compliance

6. reasons why a South African registered medicine cannot be used

7. any other information as may be required by the Authority

The Section 21 Application Form contains the following sections:

1. Applicant information (medical doctor, prescriber)

2. Information on the party requesting import (pharmacist, company, institute)

3. Patient information

4. Unregistered medicinal product information

5. Informed consent form

6. Progress report form (initial application, follow-up report in an application to extend access period, or as a final report following conclusion of compassionate use)

Applications are to be submitted electronically through SAHPRA's e-services portal: https://portal.sahpra.org.za/

SAHPRA aims to respond within 3 working days of receipt of a valid application. As noted earlier, applicants should aim to submit a new application every 6 months as that is the standard period for which compassionate use is valid, unless otherwise noted by SAHPRA.

For more information on the submissions process, please see the SAHPRA Engagement Portal's training manual for applicants.

Post-trial access/continued access

Post-trial access/continued access should be discussed when first lodging a clinical trial application, though a determination to pursue such access can be made throughout the trial. Where such access is possible, the proposal must explain how such access will occur, for example:

1. In a roll-over study, or

2. Through an expanded access programme (EAP) of the unregistered investigational product.

For roll-over studies, eligible participants will be enrolled under the same standards as the main trial. If a roll-over study was not included in the original clinical trial application submission, its proposal and protocol must undergo scientific and ethics review. The protocol must clearly outline responsibilities for investigational product costs and other requirements, including monitoring.

For expanded access programs, applicants must clearly define key healthcare roles and clarify whether the program is research or clinical treatment. It must be submitted for scientific and ethics review, with the protocol detailing cost responsibilities and other requirements.

Venezuela

Per the Norm on Medicines of Service, 01-Jul-2015, a letter of approval for either program must be obtained after submitting an application to the Rafael Rangel National Hygiene Institute (IHNRR) with the following:

Article 23. Application for Letter of Approval for Compassionate Use:

1. Curriculum vitae of the applicant doctor(s) and paramedical staff, if any (each folio countersigned and authenticated with the signature, identity card and Health Registration number for tuition).

2. Certification from a health center that accredits you as a treating physician, issued on letterhead paper and with a wet seal.

3. Informed consent of the patient(s) to be treated, as established in the Clinical Research Regulations of the Pharmaceutical Products Review Board.

4. Pharmaceutical Product Certificate if any; if not, in the opinion of the Pharmaceutical Review Board (JRPF), documented information that supports the origin of the product, indicating qualitative-quantitative formula, packaging and validity period issued by the manufacturer.

Article 21. Application for Letter of Approval for Early Access Medicinal Product:

1. Curriculum vitae of the applicant doctor(s) and paramedical staff, if any (each folio countersigned and authenticated with the signature, identity card and Health Registration number for tuition).

2. Deontological solvency.

3. Certification from a health center that accredits you as a treating physician, issued on letterhead paper and with a wet seal.

4. Informed Consent of the patient(s) to be treated, as established in the Clinical Research Regulations of the JRPF

5. The treating physician(s) must provide proof of the responsibility assumed and of having knowledge through acceptable scientific evidence of the therapeutic benefits and potential risks of the medication under study, the indication, and proposed dosage.

6. Qualitative-quantitative formula of the product issued by the manufacturer

7. Objective, faithful, documented and detailed pharmaceutical, preclinical and clinical data, related to the medication under study.

Once a letter of approval is obtained from IHNRR, an application can be made to the Directorate's Import and Export Division to authorize their entry into the country:

Form: Application for the Authorization of Medicinal Products for Compassionate Use (Legal Entity):

1. Letter of Approval -official letter issued by the IHNRR to the Autonomous Health Comptroller Service (SACS) to authorize compassionate use status

2. Proof of Payment -original and copy of proof of bank deposit or electronic transfer

Form: Application for the Authorization of Medicines of Service:

1. Letter of Approval -official letter issued by the IHNRR to SACS to authorize status of the service medication

2. Proof of Payment -original and copy of proof of bank deposit or electronic transfer

5. Orphan drug definitions

Some countries offer a mechanism to designate medicines as “orphan drugs” to aid in the development of medicines to treat rare diseases and conditions. Orphan drug designation can significantly support applications for compassionate use programs by highlighting the unmet medical need and the rarity of the condition being treated. When a drug is designated as "orphan," it signals to regulators that the treatment targets a serious, often life-threatening disease with limited or no existing therapies criteria that align closely with compassionate use eligibility.

Not all countries employ this practice of orphan drug designation, and that definitions of a rare disease/ condition vary by country.

Table 2: Orphan drug designations and rare disease definitions by market

Market	Does orphan drug designation exist?	Rare Disease/Condition Definition
United States	Yes	The disease or condition: a) affects less than 200,000 persons in the United States, or b) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will recover from sales in the United States of such drug.
European Union	Yes	The prevalence of the condition in the EU must: a) not be more than 5 in 10,000 or b) it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development.
Japan	Yes	The number of patients who may use the drug or medical device should be less than 50,000 in Japan.
Singapore	No	Not available
South Africa	No	Not available
Venezuela	No	Not available

6. Conclusion

Variability in compassionate use programs

The core principles of compassionate use are consistent worldwide, with most programs revolving around the concept of providing an unauthorized medicinal product to address an unmet medical need, typically being a severe condition or disease for which there are no satisfactory or available treatments, or for which existing treatments are insufficient. However, the procedures, timelines, and even terminology used for these programs can differ significantly from one country to another; these disparities can create confusion and deter stakeholders from pursuing such pathways.

Singapore, South Africa and Venezuela all present periods of validity that can be renewed with subsequent applications, whereas the United States, Japan and the European Union do not set regulatory limits on the duration of their programs. Singaporeand South Africa have 6 month terms while Venezuela has up to a year of validity, all with potential for extension if subsequent applications are lodged. These 3 latter markets do not currently have any orphan drug designation schemes, which other countries use to help support their efforts to justify compassionate use. The United States and Japan both treat their compassionate use programs as clinical trials and thereby subject them to similar requirements, whereas the rest of the discussed countries distinguishes them as their own unique programs. Where justified, the United States, Japan, and South Africa allow pharmaceutical companies to charge patients to recoup some of the costs incurred with the product's manufacture/development, whereas Venezuela restricts such action. Singapore's compassionate use program only operates in the context of individual patients and does not support cohort treatment.

Why pursue compassionate use?

Beyond their humanitarian value in offering hope and early access to potentially life-saving therapies, compassionate use programs confer strategic advantages to pharmaceutical companies that are often underestimated upon initial consideration. Advantages include, but are not limited to:

- Physician engagement/insights – In most cases, investigators or non-participating physicians would request to have patient(s) treated under compassionate use. A company's willingness to pursue these programs for small groups or individuals fosters trust and collaboration with the physician and can extend across their network. In addition to that, physicians can get hands-on experience with investigational therapies and provide feedback where necessary.

- Real-world data collection – Compassionate use programs are intended to include patients that would not normally be able to enroll in controlled clinical trials. As such, companies can acquire real-world evidence on the safety and efficacy of their investigational therapy, which can provide insights into endpoints such as dosing and target population.

- Public perception – Often overlooked is the value that these programs bring in the context of public perception. While it is understood that pharmaceutical companies play an essential role in developing life-saving therapies and vaccines, public perception may also be shaped by concerns around commercial interests. Compassionate use programs offer a meaningful opportunity to demonstrate a company's commitment to patient welfare. These initiatives, which involve additional costs and operational complexity, reflect a willingness to prioritize access and care over profitability. Such programs help reinforce the message that patients' needs are at the heart of responsible pharmaceutical practice.

Closing Thoughts

Compassionate use programs, though unified by a shared humanitarian ethos, emerge within a complex mosaic of national policies and procedures. The variation in regulatory frameworks—from duration limits and orphan drug support to cohort eligibility—underscores the need for sponsors to navigate each jurisdiction with precision and cultural sensitivity. Despite these complexities, these programs offer a rare chance to demonstrate patient-first values in action, in a world where pharmaceutical companies are often scrutinized for commercial motives. Utilizing compassionate use can yield great results to pharmaceutical companies on both an intrinsic and extrinsic level.

References (non-exhaustive list)

United States

1. 21 CFR Part 312 Subpart I
2. Draft Guidance for Industry: Expanded Access to Investigational Drugs for Treatment Use - Questions and Answers (Revision 1), Nov-2022 Form FDA 1571 (03/25): Investigational New Drug Application (IND), Mar-2025
3. Form FDA 1572 (04/25): Statement of Investigator (Title 21, Code of Federal Regulations (CFR) Part 312), Apr-2025
4. Form FDA 3926 (1/25): Individual Patient Expanded Access Investigational New Drug Application (IND), Jan-2025

European Union

1. European Parliament and Council Regulation 726/2004/EC of 31-Mar-2004: Laying down Union Procedures for the Authorisation and Supervision of Medicinal Products for Human and Establishing a European Medicines Agency (as Last Amended by European Parliament and Council Regulation (EU) 2019/5 of 11-Dec-2018)
2. European Parliament and Council Directive 2001/83/EC of 06-Nov-2001: The Community Code Relating to Medicinal Products for Human Use (as Last Amended by European Parliament and Council Regulation (EU) 2023/1182 of 14-Jun-2023)
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4. EMA/551338/2017: Rare Diseases, Orphan Medicines, 28-Feb-2018
5. EMA/72144/2006 Rev.: Questions and Answers on the Compassionate Use of Medicines in the European Union, 21-Jan-2010

Japan

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