Global Access to Medicinal Products: Compassionate Use Procedures

By Eileen Bedell
In most developed countries, regulation of new human medicinal products is based on confirmation of their safety and effectiveness before they are distributed commercially for use in treating patients. These laws and regulations, and the agencies that enforce them, evolved throughout the 20th century. Changes were periodically driven forward by public health crises that involved serious and severe adverse drug reactions, such as the deaths caused by elixir of sulfanilamide in 1937 and, in 1962, the birth defects in babies of mothers who were administered thalidomide. These events elicited broad support for stronger regulation to protect the public from drugs that were inadequately studied, and thus potentially dangerous.

The results in many countries were the codification and implementation of comprehensive and detailed requirements for thorough drug testing and characterization, validated and tightly controlled manufacturing processes and higher standards for confirmatory clinical evidence of the safety and effectiveness of investigational drugs. Enforcement provided authorities, and ultimately the public, with greater confidence that a thorough risk/benefit assessment of drugs would be made before approval for the marketplace. However, the strengthened regulations also resulted in longer timelines for companies to develop new drugs and for health authorities to review and approve them.

In the 1980s, AIDS grew quickly to epidemic proportions and challenged healthcare systems to provide promising treatments as quickly as possible. It was argued that an urgent and widespread medical need, such as that presented by AIDS, justified the acceptance of greater risk than normal in the evaluation of a new drug. In the US, new laws and regulations established procedures by which unapproved or conditionally approved medicines could be provided to desperately ill patients more quickly on a “compassionate use” basis. Although the term “compassionate use” does not exist in Title 21 of the US Code of Federal Regulations (21CFR), the concept is enabled in provisions for “treatment use” (21 CFR 312.34; and 21 CFR 812.36 for devices) and “accelerated approval” (21 CFR 314, Subpart H).

The need for early access to promising but unapproved or conditionally approved drugs is not unique to AIDS, and is not limited to the US. With immediate access to information via patient groups, the global medical community and the Internet, patients and physicians around the globe continue to clamor for critical new therapeutic products before approval or before a company is ready or able to introduce a product into a specific region. In many countries, regulatory hurdles such as requiring prior marketing authorization in the country of origin or local clinical data, create a delay in the availability of imported therapies. This is often termed “drug lag.”

Fortunately, compassionate use procedures have been established in many countries. Article 83 of Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency defined these procedures as making medicinal products “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 authorized medicinal product.” Depending upon the country, this principle of compassionate use is known by a variety of names, such as “treatment use,” “emergency use,” “special access,” “named-patient use,” “personal importation,” “expanded access” and “temporary authorization for use” (ATU).

Although there are individual differences among countries with regard to compassionate use procedures, there are also a number of common elements. This article does not address the US procedures, but uses Australia, Brazil and France as examples of countries with well-defined mechanisms for compassionate use of domestic and imported medicinal products. In contrast, Japan and China are examples of countries where there is a minimal regulatory framework, but where compassionate use is still possible.

Common Features of Compassionate Use Programs

Compassionate use programs in most countries, including the five cited above, share the following features.

Unregistered Product

By definition, compassionate use procedures are designed to make a product that is not registered in a country available to patients who have an urgent medical need. However, a product that is eligible for compassionate use must either be registered in another country or be in late-stage clinical trials so that its risk/benefit ratio is clearly defined. In some markets, as a condition of granting early access to a therapy, it is also expected that the marketing application for the product has already been filed or will soon be filed. For example, in France the marketing authorization application should be submitted within one year of initiation of the compassionate use request if not already filed.

Unmet Medical Need

In general, compassionate use is designed to make a product available for patients who are chronically ill, have a serious, debilitating disease or have a life-threatening condition. In all cases, there is no suitable alternative therapy in their country.
Named Patient
While the European Commission defines compassionate use as a procedure for a group of patients, the most common application is for a specific, identified patient (“named patient”). The process is often initiated by a prescription and/or a form from a physician requesting treatment for an individual patient.

Risk/Benefit Information
All countries require that risk/benefit information for the product be provided. In many instances, this can be as concise as the current prescribing information for registered products or an investigator’s brochure. However, for compassionate treatment of cohorts, comprehensive information is sometimes required. For example, in France the dossier contains many elements usually found in a marketing authorization application.

Approval and Use Timelines
In most countries, the health authority must reach a decision about a compassionate use request within a brief, defined period of time. Once initiated, compassionate use is usually for a restricted duration of treatment (e.g., six months or one year); however, there are no restrictions on applying for a second course of treatment. Interestingly, France and Brazil (expanded access program) have a minimum restriction under which the drug must be provided for a full year or for a full course of therapy.

Physician Responsibilities
The treating physician usually bears most of the responsibility for filling out the paperwork, both for health authority approval (if needed) and for import permits for drugs manufactured in another country. Other physician responsibilities (e.g., adverse event reporting) vary from country to country.

Financial Responsibilities
The costs associated with compassionate use generally fall outside standard reimbursement plans. The product is usually paid for by the individual patient or the pharmaceutical company. However, in some countries such as France, Italy and the Nordic nations, the healthcare system is responsible for the costs associated with treatment. Also, depending upon the market, import fees may be levied, which are the responsibility of the individual patient or the company.

Adverse Drug Reaction Reporting
As with marketed products, physicians are required to report adverse drug reactions (ADRs). However, specific reporting requirements vary regionally and in some countries, such as Japan, there is no mechanism to report ADRs that occur with compassionate use products.

Table 1. Compassionate Use Legislation, Guidance Documents and Websites

<table>
<thead>
<tr>
<th>Country</th>
<th>Legislation/Regulations</th>
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<tbody>
<tr>
<td>Brazil</td>
<td>• Resolution # 26/MS/ANVS, dated 17 Dec 1999&lt;br&gt;• Resolution RDC # 39, dated 5 Jun 2008&lt;br&gt;• Resolution # 251, dated 7 Aug 1997&lt;br&gt;• <a href="http://www.anvisa.gov.br/eng/index.htm">http://www.anvisa.gov.br/eng/index.htm</a></td>
</tr>
<tr>
<td>Australia</td>
<td>• Section 18 Subsec 31A(2) Reg 12A and Section 19 Subsec 31B(1) of the Therapeutics Goods Regulations 1990&lt;br&gt;• <a href="http://www.tga.gov.au">http://www.tga.gov.au</a></td>
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<tr>
<td>France</td>
<td>• Article L.5121-12 and Articles R.5121-68 to R. 5121-76 of the Public Health Code (CSP)&lt;br&gt;• Notice to applicants for Temporary Authorization for Use (ATU). November 2007&lt;br&gt;• <a href="http://www.afssaps.fr/Afssaps-media/Publications/Information-in-english">http://www.afssaps.fr/Afssaps-media/Publications/Information-in-english</a></td>
</tr>
<tr>
<td>Europe</td>
<td>• Article 83 of Regulation (EC) No 726/2004&lt;br&gt;• European Medicines Agency, Committee For Medicinal Products For Human Use (CHMP), Guideline On Compassionate Use Of Medicinal Products, Pursuant to Article 83 Of Regulation (EC) No 726/2004, 19 July 2007</td>
</tr>
<tr>
<td>Japan</td>
<td>• PFSB Notification No.0331003 dated March 31, 2005&lt;br&gt;• Notification 0331003 Dated 2005-05-31: Handling of Notifications for Importing Medicinal Products</td>
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Key Features of Compassionate Use in Brazil, Australia, France, Japan and China

Brazil
Brazil has three options for providing its population with access to unapproved products to treat diseases or conditions for which there are no effective therapeutic alternatives.

1. Humanitarian use program: enables a patient to continue therapy initiated in a domestic or foreign clinical trial after the trial has ended, if no extension trial is provided by the sponsor. The sponsor must file an application with the Agência Nacional de Vigilância Sanitária (National Health Surveillance Agency) (ANVISA) and both the sponsor and investigator must adhere to the same requirements as for regular clinical trials, including ethics committee approval and a treatment protocol. The sponsor is responsible for importing and providing product free of charge for this program.

2. Expanded access program: allows a cohort of patients to receive a product that is in Phase 3 clinical trials in Brazil or the country of origin, if that country has already established an expanded access program for the product. Via this mechanism, patients will be treated for a minimum of one year for a chronic disease or for the period needed to complete treatment for an acute disease. A treatment protocol and sufficient data for ANVISA to determine the risk/benefit ratio are required. The sponsor is responsible for importing and providing product free of charge for this program.

3. Named-patient access for personal use: permits product use based on a prescription from the treating physician and does not require preapproval by ANVISA.

France
France has two options available via its ATU plan scheme: a “nominative” ATU (authorisation temporaire d’utilisation) for a named patient and a cohort ATU for group of patients utilizing a protocol. In both instances, ATUs are granted by AFSSAPS (agence française de sécurité sanitaire des produits de santé). The government supplies the medicinal product via the healthcare institution at no cost to the patient or sponsor.

1. Under the nominative ATU, the physician and pharmacist at the healthcare institution share responsibility for preparing the application. Patient information and risk/benefit data are provided. If the product has been the subject of a previous ATU, the approval is rapid, usually within 24–48 hours. For a medicinal product that has never been evaluated, approval will take longer.

2. The cohort ATU requires a complete application consisting of three sections:
   - application
   - administrative dossier, which includes a treatment protocol and other information such as the estimated number of patients in France, any Scientific Advice previously received from AFSSAPS or the European Medicines Agency, orphan designation if granted, and information concerning compassionate use or expanded access in foreign regions
   - medicinal product dossier in Common Technical Document (CTD) format, including quality, nonclinical and clinical summary information

A cohort ATU is submitted at the same time as the marketing application or with a commitment by the sponsor to file a marketing application, usually within one year. While not a clinical trial per se, there are very similar requirements, such as informed consent for patients, study monitoring and periodic reporting to AFSSAPS.

Australia
In Australia, the Therapeutics Goods Administration (TGA) created a special access program to make critical, unapproved medicinal products available for Australian patients. In October 2002, the program was expanded to include medical devices. It is divided into two mechanisms—A and B—based on criticality. Category A patients are defined as “persons who are seriously ill with a condition from which death is reasonably likely to occur within a matter of months, or from which premature death is reasonably likely to occur in the absence of early treatment.” Category B includes all other patients; however, if other approved treatments are available within Australia, the applicant will need to justify the benefit of using the unapproved product.

For the sake of expediency, a therapy for Category A patients that is manufactured outside Australia can be imported once the request form is submitted to TGA; there is no need to wait for approval. The agency will review and approve the application within 28 days. Category B forms must be approved prior to importation of the product. TGA expects a marketing application to be filed within one year of a request as the special access program is intended to be a temporary measure pending general marketing approval of the product.
For both A and B, it is recommended that the sponsor have a treatment protocol. The treating physician assumes responsibility for the treatment, including use of an informed consent and reporting of ADRs to the sponsor. Financial responsibility is clearly specified as belonging to the sponsor and the healthcare institution.

**Japan**

Both Japan and China are examples of countries where the procedures regarding compassionate use are minimally or not codified. Many countries are similar to Japan and China in that national mechanisms may exist but are undocumented and guidance and oversight are limited.

In Japan, there are no provisions in the Pharmaceutical Affairs Law (PAL) for compassionate use. Unapproved products can be imported for “physician’s use” for specific patients through the importation laws. It is possible for a physician to import a product for a cohort of patients, not just an individual. However, the physician must obtain ethics committee approval first. As the treatment of these patients is outside the purview of the PAL, there is no mechanism for adverse event reporting.

**China**

In China, it is possible to import products for compassionate use. Article 39 of the Drug Administration Law of the People’s Republic of China includes the following enabling statement: “As to small amounts of drugs to be imported for urgent clinical need of medical institutions or for personal medication, formalities for import shall be completed in accordance with the relevant regulations of the State.”

This provision is further clarified in Article 37 of the Regulations for Implementation of the Drug Administration Law of the People’s Republic of China: “Any medical institution that urgently needs to import a small amount of drugs shall, with a Practicing License of Medical Institution, submit an application to the drug regulatory department under the State Council, and the drugs in question may only be imported upon approval. Such import drugs shall only be used in the designated medical institution for specified purpose.” Of note, “the drug regulatory department under the State Council” refers to the State Food and Drug Administration (SFDA). The individual physician and/or sponsor must develop a compelling argument based on the need to treat a serious, unmet medical need for which no other viable treatments are available in China. Obtaining permission from SFDA will rely on the support of local physicians as well as direct contact with the appropriate individuals within the agency. As in Japan, this mechanism may be applied to a cohort of patients treated via a protocol.

The regulations that enable compassionate use, along with corresponding guidances (if available) and websites, are summarized in Table 1 for these five countries and the European Union.

**Conclusion**

These five countries share a common goal: to provide their citizens access to needed therapies not yet approved in their countries. While simultaneous global development is a topic that many pharmaceutical companies embrace, in reality, there is a considerable lag between approval in the US and/or the EU and availability in the rest of the world.

The ability to access compassionate use procedural information varies. Some countries, such as France and Australia, have clearly defined legislation, accompanying guidance documents available in English and websites that are easily navigated. Others, such as Brazil, provide regulations but not always in English. For example, it is difficult to locate English-language documents via the ANVISA website. There are also countries, with China as the prime example, where it would be virtually impossible to execute a compassionate use program without the aid of in-country regulatory affairs colleagues or consultants who can interpret laws and local practices and are familiar with the appropriate officials.

**References**


**Sources**

1. AFSSAS. Notice to Applicants for Temporary Authorization for Use (ATU), Saint-Denis Cedex, France: Agence Francaise de Securite Sanitaire des Produits de Sante; November 2007.

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